



This is a digital copy of a book that was preserved for generations on library shelves before it was carefully scanned by Google as part of a project to make the world's books discoverable online.

It has survived long enough for the copyright to expire and the book to enter the public domain. A public domain book is one that was never subject to copyright or whose legal copyright term has expired. Whether a book is in the public domain may vary country to country. Public domain books are our gateways to the past, representing a wealth of history, culture and knowledge that's often difficult to discover.

Marks, notations and other marginalia present in the original volume will appear in this file - a reminder of this book's long journey from the publisher to a library and finally to you.

Usage guidelines

Google is proud to partner with libraries to digitize public domain materials and make them widely accessible. Public domain books belong to the public and we are merely their custodians. Nevertheless, this work is expensive, so in order to keep providing this resource, we have taken steps to prevent abuse by commercial parties, including placing technical restrictions on automated querying.

We also ask that you:

- + *Make non-commercial use of the files* We designed Google Book Search for use by individuals, and we request that you use these files for personal, non-commercial purposes.
- + *Refrain from automated querying* Do not send automated queries of any sort to Google's system: If you are conducting research on machine translation, optical character recognition or other areas where access to a large amount of text is helpful, please contact us. We encourage the use of public domain materials for these purposes and may be able to help.
- + *Maintain attribution* The Google "watermark" you see on each file is essential for informing people about this project and helping them find additional materials through Google Book Search. Please do not remove it.
- + *Keep it legal* Whatever your use, remember that you are responsible for ensuring that what you are doing is legal. Do not assume that just because we believe a book is in the public domain for users in the United States, that the work is also in the public domain for users in other countries. Whether a book is still in copyright varies from country to country, and we can't offer guidance on whether any specific use of any specific book is allowed. Please do not assume that a book's appearance in Google Book Search means it can be used in any manner anywhere in the world. Copyright infringement liability can be quite severe.

About Google Book Search

Google's mission is to organize the world's information and to make it universally accessible and useful. Google Book Search helps readers discover the world's books while helping authors and publishers reach new audiences. You can search through the full text of this book on the web at <http://books.google.com/>

PRACTICE OF MEDICINE

VOLUME VI

THE
JOURNAL
OF THE
ROYAL ANTHROPOLOGICAL INSTITUTE

PRACTICE OF MEDICINE

EDITED BY

FREDERICK TICE, M.D.

PROFESSOR OF MEDICINE AND CLINICAL MEDICINE, AND
HEAD OF THE DEPARTMENT OF MEDICINE,
UNIVERSITY OF ILLINOIS, COLLEGE
OF MEDICINE

FOREWORD BY

M. W. IRELAND, M.D.

SURGEON-GENERAL, U. S. ARMY



VOLUME VI

HAGERSTOWN, MARYLAND
W. F. PRIOR COMPANY, INC.

1922

**COPYRIGHT, 1922, BY
W. F. PRIOR COMPANY, INC.**

Printed in the United States of America

CONTENTS

VOLUME VI

SECTION IV: DISEASES OF THE CIRCULATORY SYSTEM

CHAPTER	PAGE
I. DISEASES OF THE ARTERIES AND CLINICAL BLOOD PRESSURE	1
By LOUIS M. WARFIELD	
II. ACUTE ENDOCARDITIS	63
By FREDERICK TICE	
III. CHRONIC VALVULAR DISEASE OF THE HEART	91
By THOMAS F. REILLY	
IV. DISEASES OF THE PERICARDIUM	205
By FREDERICK TICE	
V. ANGINA PECTORIS	253
By ALEXANDER LAMBERT	
VI. INSTRUMENTS OF PRECISION IN CARDIOVASCULAR STUDIES	281
By ALEXANDER LAMBERT	
VII. MYOCARDITIS	319
By ALEXANDER LAMBERT	

SECTION V: DISEASES DUE TO PHYSICAL AGENTS

I. HEAT EXHAUSTION	381
By L. C. JOHNSON	
II. MORBID CONDITIONS DUE TO CHANGES IN BAROMETRIC PRESSURE	395
By JOSEPH W. SCHERESCHEWSKY	

SECTION VI: DISEASES OF THE BONES AND JOINTS

I. DISEASES OF THE BONES AND JOINTS	449
By ROBERT SOUTTER	

SECTION VII: DISEASES OF THE MUSCLES

I. INFLAMMATORY DISEASE OF THE SKELETAL MUSCLES	527
By C. F. HOOVER	

CHAPTER		PAGE
	SECTION VIII: DISEASES OF THE KIDNEY	
I.	DISEASES OF THE KIDNEY	549
	By J. B. McELROY	
II.	DISEASES OF THE KIDNEY	691
	By ANTON G. RYTINA	
	SECTION IX: DISEASES OF THE BLOOD	
I.	PHYSIOLOGY, CYTOLOGY AND PATHOLOGIC PHYSIOLOGY OF THE BLOOD	739
	By JOHN H. MUSSER AND MAXWELL M. WINTROBE	
II.	THE TECHNIC OF BLOOD EXAMINATIONS	769
	By JOHN H. MUSSER AND MAXWELL M. WINTROBE	
III.	DISEASES ASSOCIATED CHIEFLY WITH ALTERATIONS IN THE RED CORPUSCLES	799
	By JOHN H. MUSSER AND MAXWELL M. WINTROBE	
IV.	DISEASES ASSOCIATED CHIEFLY WITH ALTERATIONS IN THE WHITE CORPUSCLES	861
	By JOHN H. MUSSER AND MAXWELL M. WINTROBE	
V.	DISEASES ASSOCIATED CHIEFLY WITH ALTERATIONS IN THE PLATELETS AND THE MECHANISM OF BLOOD COAGULATION	883
	By JOHN H. MUSSER AND MAXWELL M. WINTROBE	

PRACTICE OF MEDICINE

VOLUME VI

SECTION IV

DISEASES OF THE CIRCULATORY SYSTEM

CHAPTER I

DISEASES OF THE ARTERIES AND CLINICAL BLOOD PRESSURE

BY LOUIS M. WARFIELD, A.B., M.D., F.A.C.P.

Arteriosclerosis, p. 1—General definition and etiology, p. 1—General anatomy of the arteries, p. 2—Physiology of the arteries, p. 3—Etiology, p. 4—Symptomatology, p. 6—Diagnosis, p. 8—Complications, p. 8—Association with other diseases, p. 9—Treatment, p. 9—Prognosis, p. 10—Pathology, p. 10.
 Thrombo-angiitis obliterans, p. 14—Definition, p. 14—Etiology, p. 14—Symptomatology, p. 14—Diagnosis, p. 15—Complications and sequelæ, p. 15—Treatment, p. 15—Prognosis, p. 15—Pathology, p. 16.
 Syphilitic arteriosclerosis (arteritis), p. 16.
 Syphilitic aortitis, p. 17—Definition, p. 17—Etiology, p. 17—Symptomatology, p. 17—Diagnosis, p. 18—Treatment, p. 19—Pathology, p. 19.
 Aneurysm, p. 20—Definition, p. 20—Etiology, p. 20—Symptomatology, p. 22—Diagnosis, p. 26—Clinical varieties, p. 26—Treatment, p. 27—Prognosis, p. 29—Pathology, p. 29—Historical summary, p. 29.
 Thrombosis of the coronary arteries, p. 29—Definition, p. 29—Etiology, p. 30—Symptomatology, p. 30—Diagnosis, p. 31—Effects of thrombosis on the heart, p. 33—Clinical varieties, p. 35—Treatment, p. 35—Prognosis, p. 36—Pathology, p. 36.
 Periarteritis nodosa, p. 37—Definition, p. 37—Etiology, p. 37—Symptomatology, p. 38—Diagnosis, p. 38—Treatment, p. 38—Prognosis, p. 38—Pathology, p. 38.
 Clinical blood pressure, p. 38—Definition, p. 38—Technic of blood pressure measurements, p. 39—Mechanism of maintenance of blood pressure, p. 40—Average normal blood pressure, p. 42—Functional tests in relation to blood pressure, p. 44—Hypotension, p. 46—Hypertension, p. 47—Treatment, p. 56—Occurrence in various conditions, p. 57—Value of blood pressure estimations, p. 60.

ARTERIOSCLEROSIS

General Definition and Etiology.—Arteriosclerosis is an all-embracing term used to denote the various changes of an abnormal nature which take place in the arteries. It is not, however, a strictly accurate term as lesions in the aorta and large branches, confined as they are to the intima and upper layers of the media, do not show sclerosis but degeneration with calcification. Such lesions are more properly called atheromatosis. However, in the arterioles the anatomical structure is totally different from that in the aorta, so that lesions in the small vessels tend towards fibrosis and hyaline deposits in the media with intimal proliferation also. Some consider that these are distinct processes. Others consider them the same process acting upon arteries unlike in structure except for the endothelial intimal layer. Moenckeberg was convinced that the

medial calcification of the radial artery, for example, was a process quite distinct from calcification in the aorta. This view was expressed in former editions, but further studies have convinced the author that Moenckeberg's medial sclerosis is essentially the same process as ordinary atheromatosis.

These seemingly different processes are all degenerations. They are not a disease in the sense that typhoid fever or tuberculosis or syphilis is a disease. They are noninflammatory and appear to depend upon the strain put upon arteries by the heart beat plus a physicochemical change in the blood (increased cholesterol?).

In this book the term arteriosclerosis will be used to cover all changes. It is convenient, has the sanction of custom and its use will be less confusing to the reader. It is, however, to be understood that the term is much more applicable to the lesions of the arterioles where actual sclerosis is found than to the aorta where sclerosis is found only as the result of the aging of arteries.

In a certain sense arteriosclerosis, if used in connection only with lesions in the arterioles and small arteries, is a disease because symptoms arise as the result of the changes which occur in connection with the thickened arteries. Atheromatosis, however widespread, produces no symptoms unless we except the local atheromatous plaques in the coronary arteries. They do not cause the symptoms. They determine the place where clots form which produce symptoms and pathological changes.

A distinction should be made between atheromatosis and arteriosclerosis; the former is a degeneration without symptoms, the latter is also a degeneration but is accompanied by certain changes in the arterioles which may lead to symptoms.

ARTERITIS.—Acute inflammation of the arteries has never been observed except as an extension of inflammation occurring in neighboring parts. In this respect the arteries differ from the veins. The nearest approach to acute arteritis is the unusual disease known as periarteritis nodosa.

CHRONIC INFLAMMATIONS AND DEGENERATIONS.—These are common. Lesions are found varying in size and degree from small isolated patches in the intima of the aorta to extensive calcification of the coats of the large vessels and obliteration of the smaller ones. It will be convenient to describe the chronic lesions under the following headings:

1. Arteriosclerosis.
2. Thrombo-angiitis obliterans.
3. Syphilitic arteritis (arteriosclerosis).

General Anatomy of the Arteries.—In order to gain a clear conception of the lesions in the arteries, it is essential to bear in mind the anatomical peculiarities of the arteries, from the aorta to the capillary. The structure of the artery has much to do with determining the character and extent of the pathological process in which it may become involved.

The aorta and the largest branches are merely highly elastic distributing tubes. Three coats are described: (a) the adventitia, (b) the media, and (c) the intima, respectively, outer, middle and inner coats. The intima consists typically of endothelium reinforced by a variable amount of elastic tissue in which the elastic fibers predominate. The tunica media is composed of intermingled bundles of elastic tissue, smooth muscle fibers, and some fibrous tissue. The adventitia is exceedingly tough. It is usually thinner than the media, and is composed of fibro-elastic tissue. This division, while necessary for descriptive purposes, is somewhat arbitrary, as it is difficult to discover any distinct separation into layers, particularly in the larger arteries.

The muscular layer varies from single scattered cells in the arterioles to bands of fibers making up the body of the vessel in the medium-sized arteries.

There is elastic tissue in all except the smallest arteries. It varies in amount from a loose network to dense membranes. In the intima of the larger arteries the elastic tissue is formed in sheets, which, under the microscope, appear to be perforated and pitted—the so-called fenestrated membrane of Henle.

All the arteries except those one millimeter in diameter or less are supplied with intrinsic blood vessels, the vasa vasorum which enter the adventitia. The outer coat and the outer portion of the media are supplied with blood by these vessels. The intima and the inner portion of the media obtain their nourishment from the blood flowing in the artery. Lymphatics and nerves are also present in the outer and middle coats of the arteries. From the aorta to the capillaries the arterial structure undergoes profound changes which, in any particular set of vessels, although gradual, are yet definite.

The aorta is composed almost entirely of layers of elastic tissue. The intima lies on a dense membrane; the media is composed of layers of elastic tissue arranged both longitudinally and circularly, and the adventitia consists in particularly tough fibro-elastic tissue. The coefficient of elasticity of the normal aorta is physically perfect. Functionally it is the large blood-distributing tube, which, by its elastic recoil, keeps the blood in motion during the diastole of the heart. Gradually more muscle and less elastic tissue are found, so that in the radial, for example, the endothelium is seen under the microscope as a delicate line, on which a few nuclei are visible. The media is comparatively thick, and is composed of muscle cells, arranged in flat bundles, and plates of elastic tissue. Between the media and the externa, the elastic tissue is somewhat condensed and forms the external elastic membrane. "Followed toward the capillaries, the coats of the artery gradually diminish in thickness, the endothelium resting directly upon the intimal, elastic membrane, as long as the latter persists, and afterward upon the rapidly attenuating media. The elastica becomes progressively reduced until it entirely disappears from the middle coat, which then becomes a purely muscular tunic, and, before the capillary is reached, is reduced to a single layer of muscle cells. In the pre-capillary arterioles the muscle no longer forms a continuous layer, but is represented by groups of fiber cells that partially wrap around the vessel, and are at last replaced by isolated elements. After the disappearance of the muscle cells the blood vessel has become a true capillary. The adventitia shares in the general reduction, and gradually diminishes in thickness until, in the smallest arteries, it consists of only a few fibro-elastic strands outside the muscle cells" (Piersol's *Anatomy*). The capillaries, composed only of endothelium, have always been considered passive tubes without power of contraction or expansion. Krogh has presented evidence which casts doubt upon the purely passive part played by capillaries in the nutrition of organs and tissues. The structure of these minute vessels consists in a single layer of cells, the cell substance being arranged in strands running from the nuclei around the capillary. Contraction of a cell may occlude the capillary. Krogh also showed that the maximum amount of blood which can be present in a capillary area is at least 750 times the minimum. Furthermore, he demonstrated that blanching of the skin, blushing, and blanching and hyperemia of organs are dependent upon the contraction or dilatation of capillaries. Richards has shown that, just as in muscle, only a certain number of glomeruli are transmitting blood at any given moment. Further, only certain loops of a glomerulus may be open while other loops are contracted and closed. This mechanism in a kidney doing its work under basal bodily conditions enables it to take care of enormous strain put upon it, such as that of violent exercise. It has also been suggested (Dale and Richards) that there is a mechanism capable of regulating capillary tone. The lumen of a capillary is only the diameter of a red blood corpuscle, 7.5 micra, and very slight contraction on the part of the encircling cell may be sufficient to obliterate the lumen. The blood color of any tissue is actually dependent upon the filling or emptying of the capillaries, rather than upon the state of the arterioles.

Physiology of the Arteries.—The fact that the large arteries are composed mainly of elastic tissue renders them ideal as distributing channels. This is the only function which they possess. Their perfect elasticity enables them to absorb gradually the systolic force of the heart beat, and the elastic rebound of the aorta, during diastole of the heart, keeps the blood flowing evenly. In the terminal branches of the arterioles, where the muscle tissue predominates,

there is opportunity for great expansion and for strong contraction. The vasomotor fibers of the sympathetic system which leave the cord in the dorsal region, control the contraction and expansion. The large splanchnic area is capable of holding an enormous amount of blood, as are also the skin vessels in the dermis. The blood actually comes in contact with the tissue cells, with only the intervening capillary endothelium and the interchange of gases and nutrient and excrementitious substances occur in the extensive capillary area. The veins simply collect the blood and return it to the right side of the heart.

The pulmonary circulation probably acts in much the same way as the systemic circulation. No vasomotor fibers have ever been conclusively demonstrated in the pulmonary arterial branches, but there is abundant reason to believe that they are present and will eventually be demonstrated. However, the anatomical structure of the pulmonary capillaries is essentially the same as that of those found elsewhere in the body, and there is no reason to believe that they too are incapable of responding by contraction or dilatation to influences acting upon them. That they do become greatly dilated is a common postmortem observation.

As the individual advances in years, there are normal changes in the arteries which lead to thickening and inelasticity of the walls. In any estimation of the state of the arteries, especially by microscopical examination, this fact should be kept in mind. Thayer and Fabry found that the changes in arteries are definite from birth to old age. In general, the artery becomes strengthened by the development of new elastic fibers in the intima, and of connective tissue in the media and adventitia. During the third and fourth decades of life, there is also a distinct thickening of the connective tissue in the intima. By the fifth decade the deposits of connective tissue in the intima are marked, and there is an increase of fibrous tissue upon the medial side of the intima, and, in lesser degree, throughout the media. "Finally, in these sclerotic vessels, degenerative changes set in, which are somewhat different from those seen in the larger arteries, consisting, as they do, of local areas of coagulation necrosis with calcification, especially marked in the deep layers of the connective tissue, thickenings of the intima, and in the muscle fibers of the media, particularly opposite these points. These changes may progress to actual bone formation."

The mesenteric artery differs in some respects from the radial artery, but, in the main, the changes brought about by age are the same in both. There are two striking points of difference: "(1) Calcification (in the mesenteric artery) is apparently much less frequent than in the radials; (2) in several cases plaques were seen with fatty softening of the deeper layers of the intima and superficial proliferation—a picture never seen in the radial."

It has also been found that, in general, after the age of thirty-five the muscle of the media begins to exhibit fatty degeneration. After the age of fifty this condition is well marked. Furthermore, fatty degeneration may yield at this time to calcareous infiltration, or the fibers may undergo complete absorption. In very many cases it is practically impossible to draw the line between the changes which are physiological, *i.e.*, due to the aging of the tissues, and those which are pathological.

The limitation of the blood supply to the various organs, including, of course, the heart, is the natural result of the changes which take place in the arteries as age advances. Tubes which are more or less unyielding, or which are fairly rigid, cannot serve as competent distributing channels for an intermittent force-pump system. General atrophy of all organs necessarily must and does occur, and a decreased activity of the individual results. This is "old age." Some individuals who have excellent arterial tissue as an inheritance, and who have not abused the tissues, may postpone such changes as have been described for a longer period than the average. On the contrary, those who begin life with poor arterial tissue—"vital rubber," Osler has called it—and who further abuse the tissues, may be old long before the average.

Etiology.—CAUSATIVE FACTORS.—When one begins to describe the causes of arteriosclerosis, one finds many theories but few actually proven facts. Men

and women of advanced age are frequently seen who have relatively soft arteries. On the other hand, definite pathological changes in the arteries are found in infants. There can be no doubt that heredity plays a prominent rôle in the determination of arterial changes in the individual. The reasons for this are wholly unknown, but the fact remains that all do not begin life with equally resistant arterial tissue. One may thus divide the types of causes broadly into (1) congenital, and (2) acquired.

Congenital.—Possibly this type should not be separated from the general form. However, when evidences of advanced sclerosis and small aneurysms are found in infants, it is difficult to ignore the congenital origin of sclerosis. Children born of syphilitic parents show certain stigmata, among which are sclerosed arteries. Therefore, it appears to be correct to speak of a congenital form of arteriosclerosis, meaning the type in which there is transmission to the offspring of inferior arterial tissue. Changes appear so early in life that there is a gap of some years between the development of this form of sclerosis and of that caused by conditions affecting the person after birth.

Acquired.—No one cause produces arteriosclerosis. The fatty atheromatous plaques on the aorta and on the large vessels which include only the intima are caused by various febrile diseases. They have no particular significance. Infectious diseases, especially those of prolonged course and complicated with pyogenic cocci, have been regarded as factors in the production of arteriosclerosis. A study of 500 inmates of a County Poor House, with particular reference to infectious disease and palpable arteries, demonstrated this to be a negligible factor. For example, there were 252 individuals between the ages of thirty-eight and eighty years who had no palpable sclerosis; 248 with sclerosis; 147 who had serious infections, but who had no sclerosis, and 180 who had infections with sclerosis.

It is generally believed that certain products of incomplete intestinal digestion of proteins are absorbed into the blood and there produce widespread contraction of small arterioles and capillaries. This naturally requires greater effort on the part of the heart, the force of its beat is greater, the blood vessels are more violently stretched and strained and, according to Adami's terminology, "strain hypertrophy" of the vessel walls results. The vessels may here and there show lesions which are replaced by nodules of fibrous tissue. Or the whole vessel may be so strained as to produce a diffuse fibrous thickening of the media and subintimal layers. The vessel either stretches and becomes tortuous or contracts and becomes firm to the touch. In either case, it is the subject of diffuse fibrous change.

To this form of arteriosclerosis caused by increased peripheral resistance Allbutt has given the name hyperpiesis (increased "squeezing"). He considers that the hypertension (hyperpiesis) is the cause of the arteriosclerosis.

It is now generally believed that in hyperpiesis, contraction of large areas of arterioles may precede by many years the onset of changes in the arterioles. After a variable interval of time hypertrophy of the muscle occurs followed in certain cases by fibrous changes in the media. Further changes are of hyaline character rendering the artery thick and firm. Then due to some unknown cause, possibly strain, the intima hypertrophies at various areas so that the lumina of the vessels may become occluded. Under other also unknown conditions small areas of necrobiosis occur in the media of the arterioles. Many attempts have been made to find some circulating poison which might account for the general arteriolospasm but none have been successful.

The spasm is probably largely of reflex nervous origin, for, as Stieglitz has shown, sudden vasodilation with amyl nitrite will momentarily reduce a high pressure of vasospasm to a normal pressure both systolic and diastolic.

The senile form, that of pipe-stem, beaded arteries, is a concomitant of *advanced age*. It affects both males and females, the anchorite and the libertine. No race is exempt. It is not always present in those of advanced years, but it is seldom found except in the aged. Men in the fifties are seen with beaded arteries, but this is not common. In fact, the etiology of this form of arterio-

sclerosis is quite unknown. It is not the late result of hypertension. The blood pressure is normal or low. The heart is small and the muscle shows the degeneration known as brown atrophy. All the organs are atrophic and function poorly. This is expressed in the individual by thinness and slow movement. Other factors which have been blamed for arterial degeneration are alcohol, lead and tobacco. As far as alcohol and tobacco are concerned, it must be admitted that there is no proof of their relationship to arteriosclerosis. There are impressions and ideas by the dozen, but there is no demonstrable proof.

There seems to be some evidence that *lead* is a causative factor. Although no one has ever been able to produce any lesions in the arteries of animals with lead salts, yet there is abundant and very excellent evidence that arteriosclerosis is caused by prolonged contact with lead. Again, one must not be misled into believing that every worker in lead will have arteriosclerosis. This is far from the truth. That indefinable something which we call heredity plays some part. Soap and water, toothbrushes, and regular visits to dentists are factors in preventing the development of the disease.

Certain chronic metabolic disorders, such as *gout* and *diabetes*, are said to favor the development of degenerative changes in the arteries.

Muscular work, day after day and year after year, may produce arteriosclerosis of the nodular (the aorta) or of the diffuse form, or very frequently a combination of the two.

Great *mental strain* coupled with *overeating*—factors found in the lives of many of us—apparently cause early arterial degeneration. Coffee and tea are not concerned in the production of arteriosclerosis.

Where involutionary processes in the arteries are associated with advancing years, arteriosclerosis may be most extensive, and yet there may be no symptoms, inasmuch as these are dependent entirely upon the organ or organs which are affected by the change in blood supply due to the vascular sclerosis. It is doubtful whether the changes in the arteries are ever uniform throughout the whole vascular tree. Wherever they are greatest the symptoms will be most prominent.

Symptomatology.—**GENERAL SYMPTOMS.**—There is a sense of early fatigue both in body and mind. There is often an unusual intolerance of alcohol or tobacco. Vertigo is frequent; there is ringing and roaring in the ears. There may be a dull headache; irritability and somnolence, or the opposite, insomnia, are found in some cases; headache is often increased by mental effort. Numbness and tingling of the hands, arm, feet, or legs, and neuralgias, which follow the arteries, are not infrequent. All such symptoms are found in other conditions, for instance, in neurasthenia.

Mild dyspeptic symptoms are also found, such as heart-burn, belching, and a feeling of weight in the epigastrium. There is subacidity and sluggish gastric motility. Attention has been called to an unnatural pallor of the face in early arteriosclerosis. Progressive emaciation, unaccompanied by any gross pathological lesion, is also found. It is essential to keep constantly in mind the conception that arteriosclerosis is not a disease in the strict sense of the term and that its symptoms are only indications of disturbed blood supply. Perhaps the most evident and distinct symptoms are those noted in the nervous and cerebral organizations. In the former (not always to be differentiated from neurasthenia) the prodromal symptoms may be expressed in the patient by a tendency to introspection, by a feeling of regret for things done or undone, and by a curious uncertainty as to the future. Changes in mental attitude are often most noticeable to the family. An amiable man becomes irritable, a timid man bold in affairs, an even-tempered man flies into fits of anger, a tolerant man becomes jealous. Trifles are magnified until they appear to occupy the patient's whole thought. There is uncertainty of conclusion, lack of reasoning power and hesitancy in action. In cerebral arteriosclerosis a gradually progressive mental deterioration, associated with so-called "patchy memory," is the most characteristic symptom. A gradual failure of mental processes is noted. In-

sight into the mental condition is lacking, the judgment is poor, and restlessness, mental confusion and delusions of persecution possess the patient.

HYPERTENSION.—The symptoms associated with increased blood pressure in arteriosclerosis are no more distinctive than those usually found with normal pressure and beaded arteries. How often are we asked by patients, with health evident in every gesture, to examine them because recently they were told by life insurance examiners that their blood pressure was high? Such subjects are not only free from symptoms, but they stoutly affirm that they are absolutely well. Great degrees of compensated hypertension are found in patients who have no symptoms. In fact, except for the associated changes on the part of the brain, heart, and kidney, from which organs the most important symptoms arise, there are few actual symptoms due to hypertension *per se*. Among these the most constant are headache with pounding in the ears, especially noticeable in bed at night, and, occasionally, some flatulence. But dyspnea on exertion, edema, nycturia, etc., belong to cardiac and renal breakdowns.

Frequently the patient complains of failing eyesight, and the ophthalmologist, in the course of the examination of the fundus of the eye, makes the diagnosis. Bardsley considers that there are essential differences between the appearance of the fundus in simple transient high tension and in the high tension of arteriosclerosis. He makes the following distinctions:

In simple high tension:

- (1) The blood vessels have an appearance of uniform distention and fullness.
- (2) The light streak is broadened out; it may be greatly increased, apparently reaching almost the whole breadth of the vessel.
- (3) The light streak is very much brighter than normal, the brilliancy increasing with the rise of the tension, until with very high tension it becomes like bright copper wire (not silver wire).
- (4) The tight arteries indent the veins; with medium high tension, they indent them slightly, with very high tension they indent them deeply, leading to back pressure and all its consequences.

In arteriosclerotic high tension:

- (1) There is *irregular* tortuosity, especially of the smaller twigs.
- (2) There is increased brilliancy of the light streak, while at the same time the latter appears *narrower* and more central.
- (3) Irregularity of caliber and beading are sure indications of sclerosis.
- (4) General diminution in size of vessels and "silver wire" reflex show advanced sclerosis.

ANGINA ABDOMINALIS.—Although Baccelli has described a condition with this name, the symptoms are so similar to those of coronary occlusion that it would be impossible to separate them. One is led to the conviction that there is no angina abdominalis due to spasm of the abdominal arteries. Baccelli thought that attacks characterized by sudden pain of short duration in the neighborhood of the umbilicus in elderly people with flatulence, nausea, great anxiety and profuse sweating, were caused by spasm of the arteriosclerotic abdominal vessels in the upper abdomen. This may be true. No fever is said to be present. In this the attack differs from that of coronary occlusion although fever in the latter is not found always and only after the second or third day. All in all, the author would be inclined to discard angina abdominalis as a clinical entity.

THROMBOSIS OF THE MESENTERIC ARTERIES.—Ingebrigsten found 2 cases of this unusual condition at autopsy, in both of which the superior mesenteric artery was thrombosed. Neither patient had shown symptoms of such a condition during life. The vessels in both cases were luetic.

The symptoms, as a rule, are as follows: pain, vomiting, collapse, bloody stools, meteorism, rapid pulse and subnormal temperature. Thevenat and Rey report a case in a man of sixty-seven who had arteriosclerosis. The intestine supplied by the thrombosed artery formed a large abdominal tumor, which developed very suddenly. Pain and collapse with the sudden appearance of the tumor were the prominent symptoms and signs.

Diagnosis.—The diagnosis of arteriosclerosis is mainly one of exclusion. That is to say, all means should be employed to discover some other basis for the symptoms before the final diagnosis is made. Arteriosclerosis is such a comprehensive and high-sounding name that it is satisfying to both physician and patient. A man with cancer, or primary anemia, or tuberculosis of the lungs, or some neurological disease, or syphilis, etc., may have easily palpable arteries and complain of all the symptoms which characterize simple arteriosclerosis.

In palpating the radial artery to discover the presence of thickened arteries, certain precautions should be observed. In a thin person the normal artery can often be felt against the radius if one simply rolls the artery under the fingers of one hand. To palpate the artery both hands should be used. One finger presses the artery near the base of the thumb in order to shut off the pulse which may come through the palmar arch from the ulnar artery. The artery is then stripped proximally, the pulse is shut off by a finger of the other hand and the empty vessel is then palpated between the two points of pressure. The combination of enlargement of the heart downward and to the left with heaving impulse, a sharply accentuated second sound in the aortic area, and thick, fibrous arteries, is pathognomonic of arteriosclerosis with hypertension. The early signs of this condition are not easily discoverable. As a rule, these cases of arteriosclerotic hypertension occur for the most part in men who have been athletes and then have settled down to a life of business cares and mental strain. Overeating undoubtedly plays a large part in the development of the arterial diseases. The arteries of people prone to such indulgence are large and fibrous and are easily palpable. The enlargement of the heart, the increased systolic and normal diastolic pressure, and the easily palpable arteries should at once direct attention to the probable diagnosis. Until people go to their physicians for regular yearly or semi-annual examinations, these cases will not be discovered in the early stages, except the few which are disclosed in routine life insurance examinations.

It has been said by some that the combination of enlargement of the heart downward and toward the left, with a ringing second aortic sound, is pathognomonic of arteriosclerosis. This is true of the arteriosclerotic hypertension group. It holds true to some extent for the essential hypertension group, except that the heart is not as far toward the left; it does not hold true for the senile arteriosclerotic form.

Arteriosclerosis will rarely be seen by the physician except in the advanced form until men and women seek the physician for yearly or semi-annual examination as previously stated. Then the initial palpable arteries, the slight hypertrophy of the heart, and the early accented second aortic sound, together with the increased blood pressure, will direct attention to the insidious malady.

The early neurasthenia and the early mental symptoms of senile arteriosclerosis must be differentiated from true neurasthenia (nerve exhaustion), psychasthenia, pulmonary tuberculosis, cancer, etc.

Frequently the only symptom noted is failing vision, and the alert ophthalmologist makes the diagnosis from the examination of the ocular fundi.

Complications.—The complications of arteriosclerosis consist in the accidents which occur to stretched or ruptured arteries, gradual thrombosis with loss of function of the part, and myocardial changes.

Collins and Zabriskie reported a case of arteriosclerosis of the spinal cord with symptoms referable to the loss of the blood supply to the lumbar enlargement of the cord.

Occasionally the condition known as "intermittent claudication" is observed. Sufferers from this complication can walk slowly with little or no difficulty. However, if the patient hastens there is pain in one or both legs and, finally, inability to walk. After a variable period of rest the victim again recovers the use of his legs. The presumption is that the condition is due to the thickness and narrowness of the arteries, through which only enough blood passes to supply the muscles when at rest or on very slight exertion. With any extra exertion, there is a call for more blood, which cannot reach the muscles; and there is a

spasm of the arteries and relative anemia of the muscles. A period of rest, therefore, restores the circulation and the use of the muscles.

Gangrene, usually of the dry, mummifying type, is not infrequently seen in the fingers or toes, or even on the whole foot. In such cases there is *endarteritis obliterans*, or there may be *thrombo-angiitis obliterans*. Other complications which affect the brain, the kidneys, and the heart are considered elsewhere in the sections dealing with the diseases of these organs. Raynaud's disease may be associated with arteriosclerosis.

Association with Other Diseases.—Arteriosclerosis is a chronic process, does not necessarily give rise to symptoms, and is compatible with considerable activity. Consequently, it may be found associated with any disease known to us. It very materially modifies the prognosis in diseases such as pneumonia and prolonged fevers. The author believes that a distinction should be made between arteriosclerotic hypertension, the essential hypertension (hyperpiesis of Allbutt), and arteriosclerosis of the senile type. The conditions are not the same, and they are not stages of the same process. They are separate entities.

In arteriosclerotic hypertension the arteries are large and tortuous. The pulse wave is large and the vessels are elongated. In essential hypertension the artery is not tortuous, the wall is firm (feels like whip cord), and the pulse wave is not very large. In senile arteriosclerosis the arteries are tortuous, beaded, almost incompressible, due to the circular plaques of calcification, and the pulse is feeble and small. When we speak of arteriosclerosis, then, what do we mean? We cannot have in mind all three of these varieties. Our terminology is loose. We should make our terms more explicit. It seems best to restrict the term arteriosclerosis to the form in which blood pressure changes and enlargement of the heart are not present. This would confine the term to the senile form. Another form would be the arteriosclerotic hypertension. As for the essential hypertension group with arteriosclerosis, there is still a difference of opinion as to whether the sclerosis precedes the cardiac hypertrophy or is the result of the hypertrophy. Sir Clifford Allbutt holds the former view, and it seems that his conclusion has the weight of evidence in its favor. Now, since there are some experimental data which reveal a blood pressure-raising substance in the cortex of the adrenals, and since there is evidence of contraction of capillary areas resulting from circulating poisons, this viewpoint is further substantiated. Therefore, sclerosis is the initial process, while cardiac hypertrophy follows the attempt on the part of the heart to compensate for the widespread resistance to the blood flow, caused by thickened and more or less inelastic vessels.

Hence, there are three clinical varieties of general arteriosclerosis:

1. Arteriosclerotic hypertension.
2. Essential hypertension.
3. Senile arteriosclerosis without hypertension.

If we keep these distinctions in mind, we shall at least define our terms more accurately. The syphilitic form is purposely excluded from this classification. It is a special form and will be treated separately.

Treatment.—The most efficacious treatment is prevention. We cannot cure old age and we can do little for the advanced hypertension type except by giving sound advice as to diet and mode of life. Extensive propaganda is necessary to convince people that it is just as important to inventory their bodies every year as to inventory their stocks in business. We shall never be able to fulfill our obligations to the public until we succeed in persuading them of the absolute necessity for regular physical examinations. **Preventive prophylaxis** is essential.

The treatment of arteriosclerosis is so intimately connected with the treatment of hypertension that the question will be handled fully in the section dealing directly with hypertension. Likewise, the accidents resulting from sclerosis of the cerebral vessels and the results of the various other complications are discussed in the several sections dealing with those subjects.

In the senile form of arteriosclerosis, no drugs are of any special value. Usually the pipe-stem arteries are found in a routine physical examination and have little to do with the patient's illness. Diet of a simple nature, attention to the bowels and rational hygiene are the only necessities in cases of this kind.

Prognosis.—In a chronic progressive condition like arteriosclerosis, which is a natural consequence of advancing years, and which may be caused in younger life by a number of agencies, the prognosis is difficult. In the senile form, the afflicted person may live for years very comfortably. When cerebral changes begin, the prognosis is rendered more grave. However, old people with cerebral arteriosclerosis may live in asylums for several years. When hypertension and arteriosclerosis are combined in the arteriosclerotic hypertension group, the prognosis depends entirely upon the ability of the heart to carry on the circulation. Only when definite signs of cardiac decompensation appear may one begin to make a prognosis. Although the author has seen patients subject to this disease live for nine years, three years is usually a long time. Very much depends upon the circumstances of the patient—upon his ability to carry out instructions, and his willingness to coöperate with the physician. Those with financial comforts have a better chance of longevity than those who are compelled to labor from day to day.

In the type characterized by small wire arteries and very high tension, the prognosis is most uncertain. At any time and under any circumstances there may be a rupture of a cerebral vessel with consequent paralysis or sudden death. It is quite impossible to predict a cerebral accident or a failure of a heart muscle; the most that can be said is that in this type there are more cerebral apoplexies than in any other type, and, therefore, the possibility of cerebral accident is always present. Some individuals suffer from apoplexy, recover partially, and live for many years, although they retain a limp and eventually die of cardiac failure.

Pathology.—Experimentally, lesions have been produced in the aorta of animals, chiefly rabbits, by a variety of substances injected intravenously. Josué was the first to produce lesions in the media of the rabbit's aorta by adrenaline. This effort was soon confirmed. However, much of his work was discredited when it was shown that spontaneous lesions of a similar nature were found even in young rabbits. The essential lesion in the adrenaline sclerosis is degeneration of the muscular and elastic tissue of the media with consequent production of aneurysm. Some experimenters have been able to produce plaques in the aorta, affecting mainly the media, by traumatizing the vessel and then injecting cultures of *Bacillus typhosus*. Traumatism alone is not sufficient. There must be a *locus minoris resistentiæ*, plus the infective agent. Injections of *Staphylococcus aureus*, *streptococcus*, *Bacillus typhosus*, *Bacillus diphtheriæ*, barium chloride, nicotine, etc., into guinea pigs and rabbits have occasionally resulted in small lesions commencing in the adventitia, and depending upon disease of the vasa vasorum. These lesions are in no sense comparable to the arteriosclerosis of man. By repeated injections of staphylococcus into the rabbit, small plaques of fibrous thickening and fatty degeneration of the intima of the aorta have been produced. Occasionally there were small nodules of cellular connective tissue with calcification in the upper media. These changes are generally proliferative. With *Bacillus diphtheriæ* the lesions are degenerative. Injections of this organism, combined with injections of pituitrin in an attempt to produce increased blood pressure, have resulted in a vascular degeneration involving the entire aorta, the carotids to the base of the skull, the subclavians and iliacs, and, for a varying distance distally, the brachials, femorals and large abdominal vessels. The first part of the pulmonary artery is sometimes affected. The lesion is practically diffuse throughout the aorta and the vessels previously mentioned, and consists of a fatty degeneration and necrosis of the smooth muscle in a wide zone of the media, as well as in a concentration of the elastic fibers in the region affected. This produces an irregular thinning of the vessel walls and many small aneurysmal pouchings. This corresponds somewhat to the Moenckeborg type of arteriosclerosis in man, although there is a marked difference in the

medial lesions, due to the much thicker media in man. Extensive calcification also occurs throughout the degenerated zones, both in the aorta and in the large vessels.

Numerous attempts have been made to produce atheromatous changes in the arteries of small animals by feeding them large quantities of various proteins, casein, beef, egg-white. Some claim to have produced lesions, but others have utterly failed. The best evidence at present is that high-protein feeding does not of itself produce arterial lesions in laboratory animals.

Putrefying meat and the ethereal esters of bacterial putrefaction have been fed to dogs and to guinea pigs and monkeys. Some arterial changes were found, such as degeneration of the media and adventitia in connection with hyperplasia and calcification of the intima.

Critical analysis of all the changes thus far produced by the injection of poisons or by the feeding of various substances shows that no one has yet produced in animals lesions analogous to those produced in man, with the possible exception of the lesions noted above of the Moenckeberg type, produced by the combination of diphtheria bacilli and pituitrin.

Studies in the past few years have clarified to some extent the pathological changes which take place in the arteries of the human body. The process has been followed from the earliest infiltration of the coats of the vessels to the stage of calcification or aneurysmal formation. For a period the arteriosclerotic changes in the aorta were considered to be a distinct process from the peculiar calcification of the media which occurs in arteries containing a well-defined middle muscular coat. But the trend of opinion now is to look upon all these various changes as one process, the differences depending upon the anatomical structure of the individual vessel and the age of the vessel.

Thoma regarded the lesion in arteriosclerosis as one situated primarily in the media. He postulated a lack of resistance in this coat. His views are now only of historical interest.

Virchow was the first to define the atherosclerotic (the term used by pathologists now instead of arteriosclerotic) processes as a separation of the ground substance in the subintimal layer. This is caused by infiltration of plasma and is soon followed by proliferation of connective tissue. He considered mechanical factors plus a dyscrasia to be responsible for the process. Aschoff calls this the imbibition theory. He and others have shown that the infiltrating plasma contains cholesterolin esters which are deposited in the intima and may be due to one of several causes depending upon the vessel and the age period of the individual.

Aschoff considers that there are definite age periods in the life of the vessels which are highly important in determining the character of the atherosclerosis. There are three chief periods: (1) the ascending up to 35 years, (2) the summit up to 45 years and (3) the descending from that time onwards. In the descending period collagen is deposited in the coats of the vessels, the aorta and the large arteries. The coefficient of elasticity, which in the ascending period is high, is lost. The cut ends do not separate much. The aorta becomes dilated and loses its elasticity. This is senile ectasia and has nothing to do with arteriosclerosis. Atheromatosis may be in such an artery but it is not necessarily there.

Atheroma is a term applied to a process which causes swelling of the intima of the aorta and large arteries, with deposition of fatty substances (cholesterin esters); later there may be a rupture of the swollen portion with discharge of its contents into the blood stream forming the so-called atheromatous ulcer which is really not an ulcer. Extravasation of blood or absorption of blood pigment and calcification finally give to the vessel the variegated picture commonly seen at autopsy.

Scheel has made very careful measurements of the ascending, the thoracic, and the abdominal aorta, and the pulmonary artery. He found that from birth to sixty years the aorta becomes progressively wider and loses its elasticity. The pulmonary artery changes little, if at all, after thirty to forty years, and where before it was wider than the aorta, at this period it was found to be smaller. In chronic nephritis both were widened. The continuous increase of width and length of the aorta stands in reverse relationship to the elasticity of its walls.

The aorta and large branches are distributing tubes only. Even extensive lesions in these vessels have little or no effect upon the blood distribution or upon the blood pressure. It is quite different when the atherosclerotic lesions are widespread in the arterioles. Should the process be simple atherosclerosis with calcification of the media, as in Allbutt's decrescent arteriosclerosis, the organs suffer from poor blood supply but there is no increased blood pressure. On the contrary, should the arterioles be the seat of medial thickening, as in Gull and Sutton's arteriocapillary fibrosis, there is increased blood pressure and hypertrophy of the left ventricle of the heart.

One point which is worthy of emphasis is that the whole arterial tree is rarely, if ever, uniformly affected. There may be a marked degree of sclerosis in the aorta and coronary arteries with very little, if any, change in the radials. On the contrary, a few peripheral arteries may be the only ones affected. A case seen at autopsy revealed firm, tortuous cerebral vessels studded with miliary aneurysms, yet the aorta and large arteries were smooth and the radial arteries were not noted to be sclerosed during life. Likewise the coronary arteries may be the only arteries which show extensive lesions. It is not by any means possible to judge the state of the arterial tree from the sclerosis palpated in the radial artery. One can say that if the retinal arteries are seen to be the seat of some pathological process it is highly probable that the cerebral vessels are likewise affected.

The aorta, as has been said, gradually loses its elasticity as the individual grows older. This change is due to a change in the elastin which is similar wherever elastic tissue is found—bronchi, skin, etc. Old vessels are often tortuous and thick. Progressive overstretching both laterally and longitudinally with deposits of connective tissue in the intima particularly brings this about. The vessel is not weaker; on the contrary, it is often stronger in spite of the dilatation and tortuosity, but it becomes nonelastic. This is simple senile sclerosis. It is usually accompanied by hypertrophy of the left ventricle with some dilatation and increased blood pressure, the diastolic pressure rising slightly, rarely over 100 mm. Hg. This is not atherosclerosis, which is a destructive process.

For a clearer understanding of the atheromatous lesion we shall follow the description given by Aschoff, which to the writer seems the most satisfying presentation of the subject. Aschoff calls attention to certain anatomic points in the aorta. The intima possesses an outer elastic muscular longitudinal layer and an inner elastic connective tissue layer separated from each other by the elastic stria terminalis. Outside the elastic muscular longitudinal layer lies the elastic lamella which divides intima from media. The fundamental lesion in atheromatosis is loosening and widening of the cement substance in this stria terminalis with simultaneous deposition or precipitation of cholesterol esters (lipoids). Next, fat droplets are found in the spaces between the elastic and connective tissue fibrillæ of the overlying intimal layer. The intimal cells now swell and fat droplets are found in them. Finally the process reaches the endothelium. These cells swell and proliferate, causing now a definite projection into the lumen of the vessel. This is what was formerly called nodular sclerosis. Macroscopically, the aorta shows raised, irregular yellowish plaques which vary in size from a pin-head to areas several centimeters in diameter. As the stress and strain are felt more at the openings of the branches of the aorta, it is at or near these orifices that the plaques are more frequently seen. Should this process take place in childhood or puberty, or even in the early ascending period of the life of the artery, it may reverse itself and the vessel return to normal. This is particularly true of the atheromatosis of infancy. This is what Virchow called "intimal fatty change" and is the earliest lesion of atheromatosis. Atheromatosis is then a process which may be found from infancy to old age. Atherosclerosis is found only in the descending period of life.

Not infrequently such fatty infiltrations are found on the large aortic leaflet of the mitral valve. They, too, tend to disappear when the individual is still young.

The cause of this change is infiltration with cholesterolin esters from the blood plasma. The stretching of the vessels coupled with the pressure in them forces plasma into the stria terminalis where it finds itself unable to go further. The pressure loosens the cement substance. Physicochemical changes in the tissue cause a deposition of cholesterolin esters which are usually deposited in a line parallel to the blood stream, thus showing the influence of mechanical factors, the longitudinal pull.

No one factor alone can produce the lesion. There must be the combination of mechanical factors plus sufficient concentration of cholesterolin esters in the plasma. Further, there must be the peculiar physicochemical influence in the tissue to cause deposition of the esters. The cholesterolin is derived from the fat of the food. Theoretically those who eat large amounts of fat and who exercise violently should have atheromatosis. Whether this is true or not is not known to the writer. However, the reverse is apparently true. That is, absolute deprivation of fat in the diet decreases to a marked extent the lesions of atheromatosis. This was a striking observation made by all German pathologists upon the bodies of those who died during the last year of the world war and in the early post-war period.

As the life of the artery passes out to the summit and the descending period, when the inevitable changes which characterize the aging of arteries take place, the atheromatous process changes its character somewhat. The artery is firmer. The infiltrating plasma finds greater difficulty in spreading along the stria terminalis. Coupled with the swelling, necrosis sets in and the endothelium ruptures, leaving an exposed surface denuded of the smooth lining of the artery. Even before this takes place calcification has often begun in deep layers of the intima. Blood pigment, either from ruptured capillaries coming through from the adventitia or blood pigment seeping into the denuded area from the blood stream, stains the areas all the colors which blood pigment takes when it is free in the tissues. The whole inner aorta may thus be a variegated tube lined almost throughout by flat, calcified plaques. The calcification comes from the transformation of the fatty acids to form soaps, the most important of which is the calcium soap.

One might make a division of atheromatosis into alimentary, cachectic and dyscrasic. For the production of the first the fat in the plasma is the most important factor, but it alone, in the absence of the mechanical strain, is not sufficient to produce the pathologic changes in the vessels. The second is that, for example, found in tuberculosis; the third, that found in diabetes.

It is emphasized again that these lesions are not accompanied as a rule by increased blood pressure. Should atheromatosis be implanted upon the thick tortuous arteries, blood pressure would be found raised, but the increased blood pressure would be due to the thick arteries, not to the accompanying atheromatosis.

The so-called Moenckeberg's medial calcification is the same process in arteries of different structure, arteries which have a well defined muscular middle coat. The atheromatosis of the large arteries and the medial changes in the arteries with muscular coat appear at first glance to be entirely separate processes. In fact, Moenckeberg, who studied and described the lesions, holds that it is a different process. The intima is not often affected. The intact coat may lie upon a middle coat entirely replaced by calcified plaques. The weight of opinion is, however, that it is not the difference in the fundamental process but the difference in the anatomical structure which makes it appear that the two processes are unlike in their origin.

The process of wear and tear of the vessel wall is evident, not only in the intima, but also in the media, and particularly in the media of the vessels of the muscular type. Here, too, is found the loosening of the cement substance, the molecular splitting up, which is associated with the process of swelling. Here, too, arise fatty changes, above all, mucinous or mucoid softening, or better still, swelling of the physiological mucoid substance which is related to the cartilaginous matrix and exists in the media of the vessels. With these processes of fatty change and swelling are again associated the processes of calcification.

The atheromatosis of age, Aschoff's descending period, is the usual atheroma plus the diffuse sclerotic process which is characteristic of the aging of arteries. Naturally, the picture varies in the different arteries. The increased toughness of the vessel coats changes the macroscopical appearance so that, instead of having yellow spots, the color tends to grayish. But there is the same imbibition of plasma and deposit of cholesterol. Here again it must be emphasized that mechanical factors play a part. There must be cholesterol in the plasma in certain concentration and there must be physicochemical changes in the tissue.

Viewed under the microscope one sees peculiar changes in the cement substance. The connective tissue swells more than the elastic tissue. There is a tendency to overgrowth of connective tissue with hyalinization so that layer upon layer of connective tissue is formed. At first the artery looks grayish-white but later may have the faint bluish tinge of cartilage. The tissue may soften, leading to rupture of the conical necrotic area with base towards media and apex at lumen of vessel. An atheromatous abscess results. Calcification likewise takes place. The process is, therefore, the same as in puberty atheromatosis, made different by developing in old arteries which have lost some of their elasticity and have had connective tissue deposited in them.

In the arterioles at least three kinds of changes occur; a muscular hypertrophy, a fibrosis of all the coats, or a marked proliferation of the intimal endothelium. The last two are probably the same process, the connective tissue having its origin in the proliferated endothelial cells. Such a deposition of layer upon layer of cells in an arteriole and the resulting fibrosis leads to the disappearance of the lumen of the vessel, the so-called endarteritis obliterans. This, however, is not inflammation as the termination "itis" would lead one to believe.

THROMBO-ANGITIS OBLITERANS

Definition.—This is an affection occurring for the most part in male adults between the ages of 20 and 40. Formerly it was thought that the disease was confined to Russian and Polish Jews. Numerous cases however have now been seen in men of other nationalities. It is characterized by the inflammation and obliteration of both the arteries and the veins of the legs and by a subsequent canalization in cord-like remnants of the blood vessels.

Etiology.—The actual cause of the disease is unknown. It has been demonstrated that syphilis plays no rôle. Recently a streptococcus has been cultivated from the affected blood vessels which when injected into rabbits occasionally has produced a condition like the human disease. It was impossible to carry the disease from one rabbit to another. There is undoubtedly a static, mechanical factor in the onset of the disease, for the lesions always occur in the lower extremities and most frequently begin on the left side where venous stasis is most marked. Buerger states that "whatever may be the cause of the thrombosis, we feel inclined to take the view that, although the mechanical conditions that obtain in the lower extremities and the arteriosclerotic changes may be factors, some additional agent, be it toxic or otherwise, is at the same time responsible for the production of the periarteritis and thrombosis." It is a disease of *young adult life*. The patients are from twenty to forty years of age. It is a curious fact that most of the cases which have been seen have occurred in *Polish and Russian Jews*. However, these are not the only races affected. It is most frequently seen in the Free Dispensaries of large cities, where the cases are abundant. On account of the comparative youth of the subjects, the disease has been called *presenile* or *juvenile gangrene*.

Symptomatology.—Buerger's description is worth quoting in full: "The patients complain of indefinite pains in the foot, in the calf of the leg, or in the toes, and particularly of a sense of numbness or coldness whenever the weather is unfavorable. Upon examination we see that one or both feet are markedly blanched, almost cadaveric in appearance, cold to the touch, and that neither the *dorsalis pedis* nor the posterior tibial artery pulsates. When the foot becomes

warm some color gradually returns. Some patients complain of rheumatic pains in the leg. Others are able to walk only a short distance before the advent of paroxysmal, shooting, cramp-like pains in the calf of the leg makes it imperative for them to stop short. Some of these cases show the typical symptoms of intermittent claudication. After months—or, in some cases, even years—have elapsed, trophic disturbances make their appearance. It is at this stage that another rather unique symptom makes its appearance: one which gives the foot the appearance typical of erythromelalgia. When the foot is in the pendant position there is a bright red blush in the toes in the anterior part of the foot. This comes on rather rapidly, extending in some cases to the ankle or slightly above. Soon a blister, hemorrhagic bleb, or ulcer develops near the tip of one of the toes, usually the big toe, frequently under the nail, and when this condition ensues the local pain becomes intense. Such trophic disturbances may at times make little progress and last for months; sometimes, however, the skin in the neighborhood shows cyanotic discoloration, and dry gangrene of the whole toe is an early issue. Even before the gangrene, at the ulcerative stage, amputation may become imperative because of the intensity of the pain. The left leg is usually the first to become affected, although both limbs may show vascular disturbances almost simultaneously, and, when such is the case, the trophic changes, the ischemia, or the reddening, may give rise to a symptom-complex, often diagnosed as Raynaud's disease. In brief, after longer or shorter periods, characterized by pain, coldness of the feet, ischemia, intermittent claudication and erythromelalgic symptoms, evidences of trophic disturbances appear which finally pass over into a condition of dry gangrene."

Diagnosis.—From the description of the symptoms given above, thrombo-angiitis obliterans has to be differentiated from arteriosclerotic gangrene, from Raynaud's disease, and from erythromelalgia. If it is recalled that the condition appears in the lower extremities of young adults, there should be no difficulty. In erythromelalgia the arteries throb and the veins are prominent. Just the reverse is found in thrombo-angiitis obliterans.

Complications and Sequelæ.—Gangrene, the most serious complication, is in reality a part of the later stages of the disease. No sequelæ have been described.

Treatment.—In a disease in which occlusion of blood vessels is the essential lesion, there is little that can be done to cure the actual process and to establish the lumina of the vessels so that the parts will receive their blood supply.

The pain is the most distressing symptom. This may be alleviated by **hot dry applications** and by **elevating the lower extremities**. This, if kept up persistently, is probably the best method of treatment. Occasionally the so-called coal tar derivatives, **antipyrine**, **phenacetin**, etc., may be used in 10 grain (0.65 gram) doses. The new muscle spasm sedative drug, **benzyl benzoate**, in doses of from 1 to 2 drams (4 to 8 cc.), may be given. It may be necessary to administer **codeine** or **morphine** for relief of pain. Intravenous injections of hypertonic **saline solution** have been extravagantly recommended. It is doubtful whether any good has resulted. The unsuccessful cases are not reported in the literature on the subject; however, the author knows of several. The saline is used in about 1 per cent strength, and given twice daily quite warm. The amount varies. Some give 50 cc. (or about 2 fluidounces) and others give 200 cc. (or about 7 fluidounces) at one injection. **Nonspecific protein shock** has also been recommended.

A **warm climate** is distinctly beneficial. Cold increases the discomfort and pain. A dry warm climate is helpful; however, this has little real curative value. **Static electricity** and **electric light baths** with mild heat have been used. When gangrene sets in, **amputation** affords the only relief. The amputation should be performed above the area of loss of arterial pulsation. Frequently the whole lower leg, including the knee, has to be sacrificed.

Prognosis.—The disease is not necessarily fatal. Neglected gangrene may eventually prove fatal, but since the gangrene is of the dry type, it is not as apt to prove fatal as if it were of the moist type. The disease may last for years without the occurrence of gangrene.

Pathology.—The gross lesions show grayish material in the lumen of the arteries, with occasional pin-point channels cut in cross section. In younger lesions, the clot is softer and more pinkish. Still more recent lesions resemble the ordinary soft, red thrombus. The whole anterior tibial artery may be involved, including the dorsalis hallucis. The lesion may extend upward into the vessels of the thigh and suddenly cease at a branching of the vessel. Veins as well as arteries are affected. In the lower leg the posterior tibial veins are apt to suffer more than the anterior tibial. Together with the lesion of occlusion, there are periarteritis and arteriosclerotic changes. Only in the younger cases is arteriosclerosis absent. The periarteritis may be so extensive as to involve the structures immediately surrounding the artery, and the accompanying veins and nerve (if present) may be imbedded in a fibrous cord, difficult to dissect into its component parts.

Histologically the lesions may be divided into two main stages: (1) the healed or organized stage, and (2) the acute or incipient stage of thrombosis.

HEALED STAGE.—The thrombotic tissue is seen to be composed of connective tissue with sinuses of varying size and shape here and there. No elastic tissue is seen except a very small amount concentrically placed about the newly-formed vessels. "The termination of the occluding tissue in arteries and veins is often seen in the form of a rounded, convex projection pointing upward (cephalad) and lying in a practically healthy vessel wall."

THE ACUTE OR SPECIFIC LESION.—This is characteristic, and a diagnosis is possible on the basis of examination of a portion of recently affected artery or vein. An inflammatory process involving all the coats of the vessel is apparently the early lesion. Polynuclear leukocytes are found, and the clot is red. At the periphery of the clot collections of leukocytes are found; these are followed by the appearance of foci containing giant cells, endothelioid cells, or angioblasts and broken-down leukocytes. These foci undergo connective tissue replacement until only a fibrous nodule containing vessels and some pigment is left. Elsewhere the organization of the thrombosing clot is similar to that found in other conditions in which thrombosis occurs.

SYPHILITIC ARTERIOSCLEROSIS (ARTERITIS)

Syphilis is one of the few etiological factors which we feel reasonably sure does produce more or less extensive vascular change. The spirochetes have been found in the coats of the vessels, and in minute gummata in the vessels; according to Warthin, they are also numerous in the heart muscle, in cases of syphilis.

There can be no doubt that the arterial tissue in the progeny of syphilitics is liable to early degeneration. Some maintain that all juvenile arteriosclerosis is due to hereditary syphilis. The superficial arteries are uniformly thickened by fibrous tissue; they are less elastic than normally, and appear to be actually smaller than the normal. The general underdevelopment seen in many children of syphilitic parents may be the result of poor blood supply to the organs through the narrowed inelastic vessels.

In the acquired form syphilis attacks the vasa vasorum in the adventitial coat of the arteries. The earliest lesion, according to R. W. Scott, is demonstrable as a dull whitish plaque on the inner side of the aorta. This is due to the occlusion of the vasa vasorum in the adventitia. The result is ischemic necrosis of the deeper layers of the media. The intima is not involved. Following this ischemic necrosis, fibrous tissue is formed and an irregular depressed scar results which is pathognomonic of syphilitic aortitis.

The necrosed area in the media may be stretched by the pressure of the blood before it is strengthened by scar tissue and aneurysmal dilatation begins. In the vessels of the brain these small aneurysms are quite common. Rupture of the vessels is not unusual. The cerebral arteries have been found to be the site of numerous small aneurysms when all the other arteries of the body appeared to be normal. Cerebral hemorrhage in a young person who has a normal blood

pressure is always due primarily to syphilis unless different causes are found. The author has seen a number of such cases at autopsy. They are not uncommon in the large hospitals. Other lesions produced in the arteries by syphilis are aortitis and aneurysm.

SYPHILITIC AORTITIS

Definition.—This disease usually attacks the ascending portion of the aorta, is due to syphilis, and is characterized by dilatation of the arch and by aneurysmal formation accompanied by attacks of pain, dyspnea and palpitation.

Etiology.—The disease is caused in all cases by the localization of the *Spirochæta pallida* in the coats of the aorta. Although cases have been reported during the eruptive stage of syphilis, the average latent period is about sixteen years. Therefore, the disease is most frequently seen in the late secondary or tertiary stages at a time when no clinical manifestations are present. The spirochetes have been demonstrated in the artery. The disease is also found in cases of *congenital syphilis*. Longcope's youngest patient was a negro woman twenty-two years of age; his oldest, a man of sixty-eight years.

The majority of the cases occur before the age of fifty. About half occur between the ages of twenty and forty. Males are more often affected than females, the proportion being about three or four to one. The *negro race* is especially prone to the disease.

Symptomatology.—Syphilitic aortitis may be found at autopsy in cases in which there were no manifestations of its presence during life. There may be only a feeling of oppression beneath the sternum, or the patient may experience actual pain. The typical symptoms of the acute aortitis are pain, dyspnea, palpitation and tachycardia. The onset of the symptoms is apt to be paroxysmal. The patient may suddenly experience acute, oppressive pain beneath the sternum. This is accompanied by the most agonizing dyspnea. The patient sits up in bed, struggles for breath, waves his arms about, and becomes cyanotic. The heart becomes rapid and the blood pressure rises rapidly. During the paroxysm the lungs are full of piping and mucous râles. The attack ceases more or less suddenly and is followed by a rapid subsidence of the lung signs and by a decline in the systolic blood pressure. There is usually expectoration of bloody mucus. There may be several attacks daily, or these attacks may occur once a day or even less often. They are apt to be precipitated by exertion. At times there is the sensation of impending death, so characteristic of the attack of angina pectoris. The pain may also radiate toward the left shoulder and down the left arm, producing numbness.

The dyspnea is of the expiratory type. There is evidently spasm of the bronchial circular musculature in the terminal bronchioles. As a rule, the paroxysms end suddenly, leaving the patient quite exhausted.

PHYSICAL FINDINGS.—In the beginning of the process in the aorta there is no dilatation and no evidence of change which can be detected by physical methods. When the aorta has become weakened so that dilatation results, there is dulness beneath the manubrium; bronchial or tubular breathing may be heard with the stethoscope. There is often abnormal pulsation in the subclavian and carotid arteries, not infrequently accompanied by visible pulsations in the sternal notch at the base of the neck. Palpation reveals a distinct impulse.

The most important and probably the surest method of determining dilatation of the aorta is by the use of the x-ray, both with the fluoroscope and the teleroentgenograph. One should supplement the other. The characteristic lesion found by the x-ray is bulging to the right at the site of the beginning of the arch on the heart silhouette. This causes widening of the arch. Occasionally a plate will show a shadow resembling a dilatation. If this does not pulsate under the fluoroscope, it is evident that it cannot be due to a dilated aorta. Teleroentgenograms should be made in order to minimize the distortion of the shadows. At two meters the rays are practically parallel and the true size of the aorta can be ascertained.

In the cases in which the pathological process has invaded the aortic valves and insufficiency of the valves have resulted, the usual enlargement of the heart will be found with the characteristic murmurs.

Frequently there is a loud aortic systolic murmur, which is caused by the passage of the blood through a normal-sized ring, over thickened valves, into a dilated ascending arch. In such cases, the aortic ring actually becomes slightly dilated and produces the results of insufficiency of the valves without actual disease of the valves being present.

During an acute attack, accessory signs may appear. Mucous and piping râles may be noted in a hyperresonant chest. The blood pressure may show a sharp systolic rise. The presence of fever sometimes proves quite puzzling. The temperature may rise as high as 101° F. (38.33° C.) and may be either irregular or constant. The leukocyte count is not increased. The differential count may show an increase in the mononuclear elements, particularly in the small and large lymphocytes. Finally, the complement fixation reaction may help to determine the syphilitic nature of the disease. A number of studies are now available which conclusively show the relationship between apparently non-infectious dilatation of the aorta, aortic insufficiency in persons past forty years with no history of rheumatism, aneurysm, and the Wassermann reaction. Thus, in 1908, Citron reported positive Wassermann reactions occurring in 62.6 per cent of 16 cases of aortic insufficiency. Many have confirmed this relationship. In 1910 Longcope found 35 (74.4 per cent) positive Wassermann reactions among 47 cases of aortic insufficiency. In a considerable number of cases studied, the percentage of positive Wassermann tests in general cardiovascular diseases ranges from 25 to 68 per cent; in aortic insufficiency, uncomplicated by mitral disease, from 75 to 100 per cent; in aneurysm, from 85 to 95 per cent; in aortic disease in general, including aneurysm, dilatation and angina pectoris, from 75 to 88 per cent.

When the process involves the cusps of the aortic valves—as it very frequently does—the valves become thickened, shortened and incapable of closing the aortic orifice. Regurgitation of blood takes place during diastole, and gradually dilatation and hypertrophy of the left ventricle appear. The signs which are present are the ones usually found in aortic regurgitation.

It must be emphasized that syphilitic aortitis not only produces lesions in the aorta, but is also a frequent cause of aortic insufficiency in cases in which no history of acute rheumatic fever or other serious infectious disease can be obtained. *Aortic insufficiency in a person of forty or over is due to syphilis unless proved to be due to some other cause.* If this sweeping statement is kept in mind, fewer mistakes will be made in determining the etiology.

Diagnosis.—The condition must be differentiated from angina pectoris, thrombosis of the coronary arteries, rheumatic or other infections, aortic regurgitation, and aneurysm of the ascending arch. As such patients frequently have attacks of *angina pectoris*, it is not easy to exclude this disease. However, the anginal attacks are usually momentary; there is no great respiratory distress such as is seen in attacks of syphilitic aortitis. The Wassermann reaction and the x-ray examination, together with the physical signs of dilatation of the aorta, will usually establish the diagnosis. Occasionally, patients suffering from syphilitic aortitis drop dead during an anginal attack.

Attacks of paroxysmal pain, dyspnea and palpitation are unknown in aortic insufficiency of infectious origin. The case history and the Wassermann reaction will establish the diagnosis.

In *aneurysm*, the pain, if present at all, is constant, and of a dull, boring character. Other signs, such as dilatation of the pupil, irregularity of the pulse in the wrists, change in the voice, tracheal tugging, etc., aid in establishing the diagnosis.

In cases in which there is a history of *acute rheumatic fever* with aortic insufficiency and a positive Wassermann reaction, it may be impossible to determine the etiology of the cardiac lesion. Furthermore, acute endocarditis may be superimposed upon syphilitic involvement of the aortic valves.

Treatment.—The treatment of such cases naturally varies with the stage of the disease. In cases of acute aortitis in which the aortic valves have not yet been damaged, intensive antisyphilitic treatment should be instituted according to the accepted methods. It is still a matter of opinion whether **arsphenamine** or **nearsphenamine** should be given in small and frequent doses every second or third day, or whether the doses should be large and given at intervals of a week or ten days. The author prefers the less frequent doses combined with intramuscular injections of **mercury** or with intravenous injections of mercury in the form of the albuminate in conjunction with **potassium iodide** orally in doses rapidly increasing to the point of saturation. Five or six injections of **arsphenamine** or **nearsphenamine** with from twenty to thirty injections of mercury constitute one course of treatment. Nothing further should be given for a period of time varying from several weeks to two months. The course should then be repeated. Wassermann tests should be made before and after every course. It is not always possible to produce a negative test. Here one must be guided by judgment, based upon the patient's condition. It would not seem to be good practice to continue the specific treatment indefinitely when a negative Wassermann reaction cannot be obtained.

Where the case is an old one and a lesion of the aortic valves is present, the author believes that treatment should be very carefully given. It has been his experience that more harm than good results from giving intensive treatment with **arsphenamine** or **nearsphenamine**. Should symptoms such as pain and a tendency to paroxysms be present, one should use these drugs tentatively. However, the author considers that he has obtained the best results with mercury and potassium iodide. When decompensation sets in, it is combated as usual, irrespective of the cause of the cardiac lesion. For the acute paroxysm, hypodermics of **morphine** ($\frac{1}{4}$ to $\frac{1}{2}$ grain, or 0.0162 to 0.0324 gram), combined with **nitroglycerin** (1/100 grain, or 0.00065 gram), should be given.

Pathology.—Anyone who is at all familiar with the gross lesions of syphilitic aortitis has not great difficulty in recognizing the characteristic appearance of the aorta. Usually the lesions do not extend beyond the mouths of the great vessels, and the scarred and dilated ascending arch is sharply demarcated from the smooth aorta beyond. The earliest recognizable lesion is a pale gray, elevated translucent irregular patch which may measure five or more centimeters in diameter. On section, the elevated area is found to be grayish; deeper in the portion corresponding to the media there are yellowish, opaque streaks running lengthwise. The lesion may surround the vessel. Later, scarring takes place, and the areas are depressed, whitish, and have a crinkly appearance which has been likened to that of parchment. Here and there may be very thin areas the size of beads, which represent aneurysmal dilatations. The whole aorta becomes dilated and more or less rigid, due to loss of the elastic fibers. The process may extend around the orifices of the great vessels and constrict them. Only rarely is calcification found. In the extension of the process toward the root of the aorta, the valves become affected. The process extends often towards the commissures of the valves. Normally, the contact of the valves with the aorta is a delicate fine line. The syphilitic process proceeds in the commissure and the aorta immediately adjacent to it, thickening and spreading the commissure so that as much as 2 to 6 mm. may be the width of the commissure. The valves are thus shortened. They also become thickened throughout and no longer can close the aortic opening. The sinuses of Valsalva are often dilated, or only one is so markedly affected that the ring is actually dilated. The orifices of the coronary arteries are often constricted, but the process rarely extends into the arteries.

With the involvement of the aortic valves, insufficiency in their function results, with consequent changes in the left ventricle. All three of the coats are seen microscopically to be involved, although the process is believed to begin in the *vasa vasorum*. There is accumulation of round cells in the adventitia around the *vasa vasorum*. In the media the elastic fibers appear to have been dissolved, and there is necrosis with round cell infiltration. In the intima there is

an accumulation of cells, forming an actual projection into the lumen of the aorta. The areas of necrosis in the media may be extensive, and resemble true gummata. Aneurysmal dilatations are found in these weakened places. The late stages reveal scar tissue, in which are embedded fragments of elastic tissues.

ANEURYSM

Definition.—An aneurysm is a local dilatation or expansion of the coats of an artery which produces a bulging upon the external surface of the vessel. Aneurysms vary in size from minute bulgings on small arteries to huge tumors along the course of the thoracic aorta. Several forms of aneurysms are described. The most usual and convenient classification follows:

1. True aneurysm.
 - (a) Sacculated.
 - (b) Fusiform.
2. Dissecting aneurysm.
3. False aneurysm.
4. Arteriovenous aneurysm.
5. Cirroid aneurysm.

TRUE ANEURYSM.—In this variety one or more of the coats of the artery form the walls of the aneurysm. Usually at least two of the coats are found, the intima and adventitia. Portions of the media in such cases may be recognized, but this coat is usually so destroyed that it is not easily found, even after careful dissection.

Sacculated Aneurysm.—The sacculated aneurysm occurs as a definite tumor bulging out from the artery wall and connecting with the lumen of the artery by a small opening. The aneurysm grows by the accretion and coagulation of blood within the tumorous sac. This forms a solid mass; frequently the laminated clots fill the sac; the oldest clots are found farthest away from the vessel, where the color has changed to a whitish or brownish tint.

“Owing to the large area and great thickness of the fibrin deposited, and to the fact that the intimal endothelium is in most places still intact, there is little entrance of fibroblasts into the clot, and little organization goes on. The aneurysmal clot is, therefore, not converted into a solid mass of connective tissue as in endarteritis or thrombo-angiitis obliterans, but remains simply laminated fibrin. Deposits of calcium salts sometimes occur upon them, however, and tend to convert the obliterated aneurysm into a solid tumor” (Hirschfelder).

Fusiform Aneurysm.—Dilatation of the arch of the aorta is very common. It is always associated with increased pulse pressure, and in aortic insufficiency, for example, it may be very marked. There is only a degree of difference between diffuse dilatation and fusiform aneurysm, for the latter is merely a diffuse dilatation of a portion of the arch. All the coats are involved.

DISSECTING ANEURYSM.—In this form the blood extravasates between the coats of the artery. The extravasated blood may completely surround the artery, forming a tube within a tube, and may break again at some lower point into the lumen of the artery.

FALSE ANEURYSM.—This is a periarterial extravasation of blood following puncture or rupture of all the coats of the artery.

ARTERIOVENOUS ANEURYSM.—Following wounds through both an artery and its accompanying vein, there is a communication between artery and vein either directly—an aneurysmal varix—or through a sac which is formed—a varicose aneurysm. This is strictly a surgical condition.

CIRROID ANEURYSM.—This is a soft tumor composed of a large number of tortuous arteries which are branches of a common stem-artery. This is also known as telangioma. It is rare and occurs on the scalp.

Etiology.—The aneurysmal bulging begins in a rupture of one of the coats of the artery, usually the media. This rupture is caused by a weakened media plus the pressure in the artery due to cardiac systole. Theoretically, the weak-

ness of the media may be caused by arteriosclerotic lesions, by violence, or by the action of the toxins of many infectious diseases. Such primary lesions as these occasionally occur. Practically the most important single exciting cause is *syphilis*, which attacks the ascending aorta in a particular manner. (See Syphilitic Aortitis.) Long before the discovery of the complement fixation test for syphilis, clinicians and pathologists thought that all aneurysms in persons under thirty years of age were caused primarily by syphilis. In fact, the very general employment of the Wassermann reaction has demonstrated that a high percentage of aneurysms at all ages is due to syphilitic infection.

Occasionally, as the result of a violent *strain* in a diseased aorta, the intima alone may rupture, or the tear may extend into the media and the blood may force its way between the coats of the aorta. *Trauma*, such as a stab wound, may produce an extravasation of the blood, which may form a large hematoma beside or surrounding the blood vessel.

Another important factor in the production of aneurysm is the strain on the blood vessel which is produced by the *heart beat*; without this, aneurysm would scarcely be possible. At every systole the aorta is forcibly dilated. Any weak spot in its wall will therefore tend to bulge more than the normal vessel wall. Whenever there is heavy muscular exertion involving great strain, the blood pressure is much increased and the aorta is more violently stretched.

Numerous case histories lend support to this conception. Sudden onset at a definite time during a strain is frequently elicited in the history. In one case under the author's care the patient was positive that his first symptom, pain coming on suddenly, was the result of a jail punishment which consisted in his being strung up by his thumbs until his toes just touched the ground.

What Adami calls "strain hypertrophy of the aorta" probably has a place in the etiology. In this condition constant *hypertension* mechanically stretches the blood vessel, so that here and there rupture of the elastic tissue occurs, the intima is stretched, and an accumulation of cells results. This usually leads to a diffuse dilation of the arch, so that an aorta which normally measures from 5 to 5½ cm. in diameter may be 7 to 9 cm. in diameter.

An occasional cause of aneurysms in the smaller arteries is the plugging of the blood vessel by *septic emboli*. This may occur at the bifurcation of a vessel, and the embolus may lie astride of the point of bifurcation and partially or completely plug both branches of the vessel. Softening of the walls follows. Rupture may occur into the surrounding tissue, or a weakening of the coats may result, so that the vessel may bulge from the internal pressure. This embolic, or mycotic, type of aneurysm is rare.

Aneurysms are found at all ages; children are not exempt, but the ages of greatest incidence are those in which bodily activity is greatest. Hence most aneurysms are found in *men* between the ages of *thirty and fifty*.

Alcohol, tobacco, lead and other tissue poisons, *gout, diabetes, rheumatism*, are *not* important factors in aneurysm. Acute articular rheumatism, in its tendency to attack the heart valves, and occasionally the first part of the ascending aorta, is the most frequent of all the infectious diseases which contribute to the etiology.

Heredity plays no rôle except in the cases of aneurysms in children, inasmuch as hereditary syphilis is not infrequently present in the child.

Finally, aneurysms may be formed by the weakening of the blood vessel due to an extension of a neighboring *inflammation*; the coats of the vessel thereby become softened and the pressure from within produces a bulging at the weak spot in the vessel. *Men* are much more prone to aneurysms than women, the proportion being about 5 to 1; and the *negro race* is especially affected, due to the frequency with which negroes contract syphilis, and to the character of their work as stevedores, laborers, miners, etc.

Any artery may be affected, but the thoracic aorta and the popliteal artery lead in the incidence of aneurysm. Thus, in a series of 530 cases (Crisp) the arteries were affected as follows:

Thoracic aorta.....	175
Popliteal artery.....	137
Femoral artery.....	66
Abdominal aorta.....	59
Carotid artery.....	25
Subclavian artery.....	23
Axillary artery.....	18
External iliac artery.....	9
Cerebral artery.....	7
Common iliac artery.....	2
Posterior tibial artery.....	2
Gluteal artery.....	2
Pulmonary artery.....	2
Brachial artery.....	1
Subscapular artery.....	1
Ophthalmic artery.....	1

Aneurysm may be multiple; two or more may occur along the aorta or along any artery.

Symptomatology.—It is convenient to divide aneurysms into those characterized (a) by signs, and (b) by symptoms. The former are for the most part found in the ascending arch, while the latter include the aneurysms of the transverse arch. The symptoms vary greatly. The growth of the aneurysm *per se* does not as a rule produce any symptoms. All of the distress of which the patient complains results from pressure of the aneurysm upon adjacent structures. An aneurysm which grows upward and to the right, or which bulges to the right from the ascending arch or to the left from the descending arch, may reach an enormous size, with little or no discomfort to the patient. On the contrary, a very small aneurysm, involving the transverse arch or the first part of the descending arch, may press upon the neighboring structures to such an extent that it gives evidence of its presence by symptoms long before objective signs can be elicited.

In probably one-half of the cases an aneurysm near the sinus of Valsalva is free from symptoms and gives evidence of its presence only when death suddenly occurs due to perforation into the pericardial sac. Dissecting aneurysms have been known to rupture into the pericardial sac. Even young children are not altogether exempt. Death may not be sudden. The patient may live for several hours after rupture. In many cases the heart becomes dilated and hypertrophied through the insufficiency of the aortic valves, which may be involved in the syphilitic aortitis; or the aorta just above the valve may become so stretched by the growth of the aneurysm that a dilatation of the ring occurs and a relative insufficiency results. Signs of heart failure may, at any time, complicate the aneurysm. Indeed, death from heart failure may be due primarily to an aneurysm which presented no symptoms, and which was overlooked because, when the patient came under observation, the cardiac decompensation signs, cyanosis, edema of lungs, edema of the legs, enlarged liver, irregular pulse, etc., dominated the picture. Syphilis, as shown by Warthin and others, attacks not only the aorta but the heart itself, inducing widespread necrosis, which leaves a scar formation when healed. Hence the heart is in a weakened state and prone to break down upon comparatively light strain.

Aneurysms occur for the most part in robust, full-blooded individuals. They may advance rapidly in size and cause loss of appetite, loss of weight, interference with sleep, and emaciation. Bronchopneumonia may terminate the patient's misery, or acute compression of the trachea or of the esophagus may cause death. Of the special symptoms, the most constant is *pain*, which may be either of a dull, boring, constant character or paroxysmal. There may be only a feeling of weight or oppression beneath the sternum. Anginal attacks may occur, the pain radiating down the right or the left arm. Pain in the chest is

such a constant symptom that it should arouse suspicion of aneurysm when the pain cannot certainly be accounted for by some obvious condition.

When the aneurysm involves the descending portion of the arch, the pain is apt to be constant and excruciating, due to the erosion of one or more vertebræ and the consequent pressure and inflammation around the roots of the nerves. Often the pain is referred to the front of the chest or to the upper part of the abdomen in the distribution of the nerves. Pain may be the only symptom of the disease and may simulate the pain of gastric crises in *tabes dorsalis*.

Shortness of breath on exertion, similar to that produced by cardiac disease, may be the initial symptom, or it may accompany the pain. The dyspnea is frequently manifested only upon lying down at night. Other symptoms involve special structures which are pressed upon by the tumor.

On the left side the recurrent laryngeal nerve loops around the transverse portion of the arch of the aorta. On the right side the nerve loops around the subclavian artery. The high position of the right nerve protects it to a great extent from injury. However, when an aneurysm involves the first part of the transverse arch and the innominate artery, the nerve is involved in the sac and symptoms characteristic of pressure are produced. On the left side the nerve is exposed to injury much more frequently, due to the greater incidence of aneurysm of the transverse arch. Irritation of the nerve may produce spasm of the larynx, and interference with swallowing; it also gives rise to a peculiar cough described as "brassy," or as the "goose" cough. It is so distinctive that one knowing the characteristics of the cough can frequently detect the case of aneurysm among the patients in a large ward.

The voice is husky, and when the nerve is destroyed, the vocal cord is completely paralyzed and lies in the so-called cadaveric position. The right cord may then be brought across the median line in an effort to produce phonation. However, in such cases huskiness is so great that only whispering is possible. While the left cord is the one commonly paralyzed, it must not be forgotten that the right cord, for reasons given above, may be as completely paralyzed and may produce the same symptoms as paralysis of the left cord.

The phrenic nerves lie just back of the pericardial sac, but are not often involved in aneurysm. Should they be irritated, hiccup or spasm of the diaphragm may be present. Irritation or paralysis of the sympathetic fibers at the root of the neck may produce dilatation or contraction of the pupil; this usually occurs on the left side. The pupillary change may also be due to changes in the blood supply. Usually there is slight dilatation. The response to light is present. As syphilis is also responsible for irregular pupils, the light reflex will differentiate the cause of the irregularity.

Difficulty in swallowing may be due to a transient spasm caused by the irritation of the recurrent laryngeal nerve, or it may be persistent when the aneurysm actually presses upon the esophagus. Usually the patient thinks he feels a lump in his throat, and solid food may seem to stick momentarily. At autopsy, the esophagus has been found to be stretched to twice its width and firmly adherent to the aneurysmal sac; yet during life the condition had produced no symptoms. Everything depends upon the manner in which the tube is compressed. Even in large aneurysms the esophagus is merely pushed aside and not compressed against the vertebræ or ribs. It is well to bear in mind the fact that apparent strictures of the esophagus may be due to the pressure of an aneurysm.

Cough is a very common and often a most distressing symptom. It is dry and hacking, and may be so persistent that the patient has no rest day or night. Such a cough is usually due to the pressure of the aneurysm upon the trachea, which is often eroded; ulceration of the mucous membrane has also been found. Dyspnea may be due to the actual narrowing of the trachea. One or the other main branch may also be compressed; cough is likewise the chief symptom. Often the patient can tell from which side the cough arises. Imperfect aëration leads to the collapse of portions of a lung, or, in rare cases, to the collapse of a whole lung.

When the aneurysm is large, it may actually compress the lung and cause collapse with eventual fibrosis. While a certain amount of collapse occurs in all aneurysms of the descending arch and thoracic aorta, it is rarely sufficient to cause symptoms.

Interesting collateral circulation is frequently caused by the pressure of the aneurysm upon the veins. The space through which the structures above the heart pass is small and many large vessels are found there. Almost any tumor will produce some compression of the veins. Rarely is one of the large veins, for example, the superior vena cava, obliterated, but the subclavian and jugular veins, particularly the left one, are often compressed to such a degree that the blood has to find its way from the head and arm to the inferior vena cava through the anastomosis of the mammary with the epigastric veins. One side of the chest may show dilated and tortuous veins with the current flowing from above downward. Fulness in one side of the head may be complained of, and there may be slight edema of the arm.

PHYSICAL FINDINGS.—Inspection.—The physician who trains his eye so that he sees with his cerebral cortex and not alone with his retina will make many diagnoses of aneurysm by inspection. This method should never be neglected. It is of prime importance in diagnosis. The patient should be stripped to the waist and placed in a good light. Osler often called attention to the number of aneurysms which were unrecognized because of the examiner's habit of pushing the shirt up under the chin. The most important area of the chest is thereby either covered or has a shadow thrown over it.

The area from the base of the heart to the sternal notch is the region in which most signs are found. Visible, expansile pulsations, synchronous with the systole of the heart, are to be anticipated. The characteristic of the aneurysmal tumor is expansibility. A pseudo-expansile pulsation is often seen in the course of the abdominal aorta when a solid tumor overlies that vessel. The first and second interspaces to the right or to the left of the sternum are the commonest sites of abnormal visible pulsation. If one looks down the patient's back, one may see pulsation near the lower angle of the scapulæ.

This pulsation must not be confused with that of the conus of the right ventricle which is found in the second left interspace. This is common in children and in thin-chested persons. Throbbing of the aorta in anemic states, in aortic insufficiency, and in Graves' disease may stimulate aneurysm. Occasionally a pleural effusion may so dislocate the heart that there are pulsations in unusual places. If one bears these in mind and exercises reasonable care, there should be no difficulty in diagnosis.

The slight inequality of the pupils in connection with the reaction to light often directs attention at once to some intrathoracic trouble. Dilated veins on one side, abnormal pulsation of the vessels of one side of the neck, and edema of the arm or upper chest, are easily seen if a careful inspection is made. A diagnosis of aneurysm can be made in many cases by inspection alone. Other methods of examination are only confirmatory.

Palpation.—A visible pulsation can usually be felt. There is a distinct push on the palpating finger. A thrill systolic in time may be felt, and the closing of the aortic valve is felt as a distinct thump, the diastolic shock.

In the abdomen it is often very difficult to determine whether or not a pulsating tumor is expansile. Palpation with both hands, one on each side of the tumor, will help to determine the question. The pulsation must be expansile.

(a) *Peripheral Arteries.*—When an aneurysm involves the arch so that the orifices of one of the three great branches are included, there may be definite palpable changes in the pulse waves of the carotids or radials on the two sides. Both delay and decrease in size of the pulse wave are found separately or together. The common practice of feeling one radial when making an examination is to be deprecated. The practice of grasping both radials, one with each hand, would save much confusion in diagnosis. Conditions other than aneurysm may produce changes in the radials or carotids, but these will be more easily eliminated when attention is directed toward the possibility of aneurysm.

(b) *Tracheal Tug*.—This is a sign which was described by Oliver in 1878. It is due to the adhesion of the sac to the trachea; this in turn transmits the impulse to the trachea. It is one of those accessory signs described in so many diseases which has absolutely no bearing on the diagnosis. To elicit this sign the examiner directs the patient to incline his head slightly forward. The cricoid cartilage is then firmly grasped by the examiner, or the finger is placed in the cricoid notch, and an upward pull is made. At each systole, if the sign is present, a tug may be felt. It is interesting, but has little or no diagnostic value.

Blood Pressure Examination.—The blood pressure is usually equal in both brachial arteries. In aneurysm there is often a difference of from 10 mm. to 20 mm. in the systolic pressure on the two sides. The diastolic pressure is not affected. Here again it is of distinct value to take the blood pressure on both arms at the first examination.

Percussion.—Many aneurysms of the arch are so situated that they modify the normal clear percussion note over the chest and back. Normally, the whole upper chest above the third rib, including the mediastinum, has a resonant percussion note. A tumor of moderate size may impair the note; if the tumor is large, it may cause a flat sound below and on both sides of the manubrium for a variable distance. The percussion stroke should be exceedingly light, so that the smallest possible resonating area may be set to vibrating. The dullness due to aneurysm of the arch is continuous with the cardiac dullness. In the back there may be a perceptible change of percussion note over a large aneurysm. The pitch of the note will depend upon the amount of lung tissue which lies between the tumor and the chest wall.

Auscultation.—Various sounds are heard over aneurysms. Over the aortic area there is often a long systolic murmur of a rough rasping character, transmitted far along the branches. When aortic valves are incompetent, a low-pitched diastolic murmur is heard. The palpable diastolic shock is heard as a ringing sound over the aorta. At times there may be a continuous hum, "bruit de diable," and again no sound will be heard at all.

A small aneurysm in the anterior mediastinum may give a bronchial or tubular quality to the respiratory murmur when the stethoscope is placed on the skin over the manubrium. Tubular breathing can practically always be heard in aneurysm of the arch, but often the loud heart and vessel sounds so dominate the auscultatory phenomena that the breath sounds are obscured. The author has found that auscultation over the manubrium is a valuable help in diagnosing tumor masses in the mediastinum.

X-ray Examination.—The study of aneurysm is not complete unless the fluoroscope and radiograph are used. This is not an implication that one cannot make a diagnosis of aneurysm without the ray; diagnoses were made successfully long before Crookes discovered the cathode emanation and before Roentgen made the x-rays practicable in diagnosis. However, in every case of suspected aneurysm a careful x-ray examination should be made. Only in this way can many aneurysms be surely discovered. The fluoroscope is of more diagnostic value than the plate. The latter only reveals a tumor, which may be an aneurysm. But with the fluoroscope one can see the expansile pulsation in a tumor above the heart. A healed sacculated aneurysm full of solid laminated clot would behave like any solid tumor. In such a case the presence of enlarged glands in the axillæ or neck would assist in determining whether the picture was one of solid aneurysm or of mediastinal tumor. In order to obtain the true size of an aneurysm teleroentgenograms or an orthodiographic tracing should be made. The ordinary plate taken with the tube at a distance of from twenty-four to thirty inches increases the size and distorts the shadows of the chest organs.

DEVELOPMENT OF THE ANEURYSM.—An aneurysm once formed grows, as a rule, toward the regions of least resistance. In the course of its growth it may come in contact with the bony structures or with the softer parts of the body. It is not uncommon for the aneurysm to erode the ribs or sternum and to point toward the surface of the skin. The erosion of the ribs and sternum is

PRACTICE OF MEDICINE—Fice. These new pages 1-61 take the place of the old pages 1-66, Vol. VI. Discard the old, insert the new.

usually painless. However, aneurysms of the thoracic aorta may erode the vertebræ and give rise to great pain. The trachea, bronchi, and esophagus may also be eroded, and the aneurysm may bulge into the lumen of any of these structures. The direction which the aneurysm takes is to a large extent determined by its situation on the arch. Thus, aneurysms of the ascending arch point to the right and upward in the direction of the blood stream; those of the transverse arch point upward and backward; and those of the descending arch point upward and toward the left.

RUPTURE.—About one-half of all deaths from aneurysm of the arch are the result of more or less sudden rupture. This may occur through the chest when erosion has brought the sac just beneath the skin; or it may break into the pericardial sac, the trachea, the bronchus, the esophagus, a large vein, etc. The aneurysm in the abdominal aorta rarely ruptures into the duodenum. A case with autopsy findings was reported in which the abdominal aneurysm in a previously healthy woman ruptured into the tissues of the retroperitoneum. There was sudden acute abdominal pain and collapse. The patient rallied temporarily and died twelve hours later of further hemorrhage.

Death may be sudden, or it may be delayed for several hours. There are several cases on record of rupture into the pleural cavity in which the patient survived one or two days. Oozing of blood from an aneurysm which has eroded the ribs or sternum is not at all uncommon. The skin becomes discolored and finally ulcerates. Oozing begins through a fungus-like, spongy opening in the aneurysmal sac. It may continue for a number of days and cease spontaneously. Suddenly there may be a gush of blood, and the patient may die in a few minutes. High blood pressure, resulting from strain, is often the determining cause in a rupture.

Diagnosis.—In spite of the number of symptoms and signs which may occur in aneurysm of the thoracic aorta, the diagnosis is often difficult. Substernal pain alone may be due to simple dilatation of the aorta and must not be confused with that of aneurysm. This latter is to be differentiated from (1) solid tumors of the mediastinum, (2) dilatation of the arch, (3) pulsating encapsulated empyema in the upper chest, (4) pulmonary tuberculosis, and (5) mitral stenosis.

If these conditions are borne in mind and it is remembered that the tumor must be expansile, mistakes may be avoided. In suspected cases the x-ray is invaluable. Occasionally an aneurysm is so far healed that it is more or less solid and does not expand at every cardiac beat. In such a case the smooth globular outline of the tumor and its close association with the aorta should be sufficient for diagnosis. Occasionally a tortuous subclavian artery or an enlarged jugular bulb may simulate aneurysm. These conditions should cause no great difficulty in diagnosis if care is exercised in the examination.

Aneurysms of the arch are sometimes overlooked through carelessness in examination and failure to keep in mind the constant possibility of this condition. Careful percussion and auscultation over the manubrium in every case will prevent many errors. Aortic insufficiency is so frequently associated with aneurysms of the ascending arch that the aneurysm is apt to be submerged in evident cardiac lesion. Here, again, care is essential and the x-ray is a valuable aid.

Clinical Varieties.—**DISSECTING ANEURYSM.**—In this type of aneurysm there are no symptoms which are distinctive. In the great majority of cases the condition is found only at autopsy. Occasionally the aneurysm perforates and death results. In one such case in a girl twelve years old the aneurysm perforated into the pericardial sac. The aneurysm forms through a fracture of the intima and the media, in which event the blood works its way between the media and the adventitia. After a time, endothelium may form in the wall of the false channel.

ARTERIOVENOUS ANEURYSM.—Communication between an artery and a vein is not uncommon in the peripheral arteries where perforating wounds, especially bullet wounds, can penetrate both artery and vein. In the late World

War there were a number of such aneurysms; they were usually found between the femoral artery and the vein. The diagnosis is not difficult.

A much rarer situation is in the thorax between the aorta and superior vena cava. Death usually follows in a few hours, but the patient may survive and live for several months. The rupture is ushered in by sudden intense dyspnea, cyanosis of the face, and distention of the veins of the neck. A tense edema rapidly supervenes, and dilated veins quickly form over the thorax and end abruptly at the attachment of the diaphragm. Over the perforation site, which is naturally near the aortic cartilage, a thrill is usually felt, and on auscultation a continuous murmur is heard; this increases in intensity at every systole. "Perforation into the *pulmonary artery* is attended by sudden and severe dyspnea, which is followed by cough and occasional blood-streaked sputum. A thrill over the pulmonic area is occasionally present. The most characteristic physical sign is a continuous, roaring murmur, with a systolic intensification; this is heard over the pulmonary area. Perforation of the pulmonary artery is not, as a rule, immediately fatal. A period of weeks or even months may elapse before death occurs" (Landis).

ANEURYSM OF THE ABDOMINAL AORTA.—Aneurysm of the abdominal aorta is not so common. At the Milwaukee County Hospital, not one case has been seen among the last 500 autopsies; in the wards, among the admissions of a five-year period, 9,584 patients, not one case has been seen, although during this time there were 54 thoracic aneurysms. This type is said to constitute from 10 to 14 per cent of all aneurysms. Pain is a prominent symptom. It may simulate the pain of gastric ulcer. Erosion of the spine is common. Under such circumstances the pain is constant and excruciating. Large doses of morphine do not cause it to cease although they usually alleviate it to some extent. A patient with large eroding abdominal aneurysm is truly a pitiable sight.

Violent pulsation of the abdominal aorta is a frequent condition, particularly in neurotic persons. The shock may be so great as to jar the bed in which the patient is lying. The relaxation of the abdominal organs, the looseness of the retroperitoneal tissue, the low peripheral resistance, are probably all factors in producing the violent pulsation. Solid tumors, such as may occur in the stomach, may lie upon a bounding aorta and produce on inspection an appearance not unlike that of aneurysm. The most common seat of the aneurysm is around the celiac axis or near the branches leading to the kidneys.

The difficulty in diagnosing the aneurysm rests somewhat in its location high up behind the lesser peritoneal cavity. *Unless there is a tumor which can be grasped between the fingers of one or of both hands and felt to expand in all directions at every heart beat*, one is not justified in making the diagnosis of aneurysm. No mistakes are made by adhering rigidly to that rule. It is surprising how difficult it is at times to decide whether or not the above criteria are fulfilled in any particular case.

The aneurysm may be fusiform, sacculated or dissecting. There may be a difference in the time of the femoral beats; the beats in both arteries may be delayed appreciably; or, if the aneurysm is large, it acts as a catch-basin for the pulse wave and there is no femoral pulse, and the blood flows through in a constant stream propelled by the recoil of the large reservoir sac on the aorta.

ANEURYSMS OF OTHER ARTERIES.—Aneurysm of the ophthalmic artery or of the vertebral or basilar arteries is rarely found. The diagnosis is practically impossible. Aneurysms of the arteries of the arms and legs present no especial problems. They are largely of surgical interest. The commonest is aneurysm of the popliteal artery.

Treatment.—The medical aneurysms, so to speak, are in almost all cases the result of syphilitic aortitis, so that the prophylaxis of aneurysm is the prophylaxis of syphilis. If there is no syphilis, there is no aneurysm; or if syphilis is absolutely cured, there is likewise no aneurysm. Therefore, in order to prevent the development of aneurysm, it is necessary to go back years in the life of the individual. Once the damage is done, it is irreparable. Aneurysms may heal spontaneously by laminated clotting within the sac, but this is pos-

sible only in the case of those aneurysms in which there is a small opening and a large sac. There can be no spontaneous healing where the opening is large or where the aneurysm is fusiform in type.

GENERAL MEASURES.—Most patients suffering from an aneurysm present themselves on account of pain or cough or both. Cough mixtures are useless. The patient should be **put to bed**. This reduces the number of pulse beats and lowers the blood pressure. At the same time **potassium iodide** should be given twice or three times daily in doses of 15 grains (1 gram). The patient should be kept in bed several weeks and should be given a diet of about 10 calories to the pound weight of the patient.

In 1874, Tufnell revived the **rest and starvation** treatment. He gave ten ounces of solids and ten ounces of liquids daily for several weeks. The patient must maintain a **horizontal position**, not rising for anything. No water is allowed. Tufnell's diet formula follows:

Breakfast	{ Bread and butter	60 grams (2	ounces)
	{ Milk	60 cc. (2	ounces)
Dinner	{ Meat	60-100 grams (2-3½	ounces)
	{ Milk	75-125 cc. (2¾-4¼	ounces)
Supper	{ Bread	60 grams (2	ounces)
	{ Milk	60 cc. (2	ounces)

This is exceedingly rigorous and of doubtful value. However, limitation of the diet is essential. **Calcium lactate** and **gelatin** injections have been given during this rest period with doubtful results. After the rest treatment, the patient should lead a very quiet life, throwing as little strain as possible upon his blood vessels. The question naturally arises: should antisiphilic treatment be given? In many cases the Wassermann blood serum reaction is strongly positive. In such cases it seems rational to give intramuscularly from 0.06 to 0.12 gram (1 to 1.5 grains) of **mercury salicylate** weekly for five or six weeks. A period of rest should follow; then a further course should be given, and the intervals between treatments should be lengthened until the patient takes only one or two courses of treatment a year. The blood should be controlled by the Wassermann reaction, although it is not always possible to produce a negative reaction. The patient must be kept under observation, if possible, so that the symptoms can be controlled as they arise.

Arsphenamine and **neoarsphenamine**, if given, should be carefully administered. It is advisable to commence treatment with small dosages, *e.g.*, 0.3 gram (5 grains), so that the effect of the treatment can be studied. More harm than good may result from too intensive treatment. In some of those cases the Wassermann never becomes negative. Hence it is obviously futile to continue giving arsphenamine. Much judgment is required in treating such cases and no rules can be formulated.

Several years ago **wiring** of an aneurysm had quite a vogue. About ten feet of specially prepared coiled wire were introduced into the sac through a special needle. The free end was then connected to the anode of a galvanic battery. A pad under the patient's back was connected with the cathode terminal. A current of 10 milliamperes was administered for thirty minutes. The current was then increased to 20 milliamperes for ten minutes if the patient could stand it. No constant results were obtained and the method seems to have fallen into disuse. It was applicable only to true sacculated aneurysms in which spontaneous clotting was favored. In a case at autopsy the author saw ten feet of wire coiled in the transverse arch directly in the blood stream.

In case the aneurysm is eroding the vertebræ and causing intense pain, symptomatic relief with **opiates** is all that can be accomplished. The fear of creating a morphine habit should not prevent the physician from relieving the actual pain. Abdominal aneurysms may be amenable to surgical treatment, but, as a rule, they occur high up near the celiac axis and are inaccessible to surgical intervention.

Prognosis.—Aneurysms may reach a certain size and then become stationary; or in rare cases, they may heal spontaneously. For the great majority of cases, the course is from one to five years, although the aneurysms may remain stationary and be compatible with a fairly active life for twenty or even thirty years.

Rupture, either through the chest wall after erosion or into some neighboring structure, is the most frequent mode of death. This has been discussed above. However, in about 45 per cent of cases, death is due either to pressure upon important nerves and blood vessels or to changes which take place secondarily as a result of such pressure. Once the aneurysm begins, the usual course is progressive growth, slow or rapid, depending upon many circumstances.

Pathology.—Aneurysms may be produced by violent strain alone in an aorta already thinned and weakened by arteriosclerosis. It is exceedingly doubtful whether any sudden rise of pressure could rupture a normal artery. It has been demonstrated that the aorta will withstand a strain ten to twenty times greater than the normal systolic pressure, before rupturing. No such pressure could occur during life. Syphilitic aortitis precedes the formation of aneurysm in the great majority of cases. The lesion occurs first in the media when necrosis takes place; elastic fibers are dissolved and round cell infiltration takes place. The intima proliferates and the adventitial vessels, the vasa vasorum, develop new capillaries. Scar tissue finally heals the wound. Should the process be extensive, dilatation of the arch is certain to result, for the artery is being stretched eighty or more times a minute, and is thereby weakened. A sudden rise of blood pressure at a very weak spot may produce a bulging. The extent of the pathological process in the aorta and blood pressure determine the further development of the aneurysm. No clotting can occur in a fusiform aneurysm. Clotting and spontaneous healing may take place in a sacculated aneurysm. Dissecting aneurysms at times heal by clotting just as do sacculated aneurysms. The process is the same. There are no fibroblasts and hence there is no scar tissue. The clot becomes laminated and is usually of putty-like consistency when firmest.

Historical Summary.—Aneurysm has been known since the time of Galen, who, however, recognized only the traumatic variety. It was Vesalius (1543) who seems to have been the first to recognize and even to diagnose thoracic aneurysm. Ambroise Paré suggested the rôle of venereal disease. The relation between syphilis and aneurysm was demonstrated by Lancisi as long ago as the early eighteenth century. Nearly a century later Scarpa laid the foundation of the modern conception by demonstrating that the weakening of the middle layer of the artery was the important mechanical factor. The discovery of the *Spirochaeta pallida* by Schaudinn in 1904 and the demonstration by Warthin and others of spirochetes in the wall of the aorta, proved the accuracy of the generalization of the relationship of syphilis to aneurysm which was pronounced two and a half centuries ago.

THROMBOSIS OF THE CORONARY ARTERIES

By far the most serious results of atheromatosis and arteriosclerosis arise from disease of the coronary arteries. It might here again be emphasized that arterial lesions may be confined to a very small group of arteries in one or more organs, and that even when the arterial lesions are found in only one organ they are not uniformly distributed in all the arteries of that organ.

Definition.—Thrombosis of the coronary artery is the sudden occlusion of one of the main branches, either by a thrombus or by an embolus. The two main coronary arteries, the right and the left, or posterior and anterior, arise from openings behind the aortic valve cusps. The right supplies the right ventricle and auricle and sends branches to the posterior part of the interventricular septum. The left branches shortly after its origin, one branch going towards the left into the auriculoventricular groove, supplying the left auricle and the posterior portion of the left ventricle, and the other large branch descending near the interventricular septum supplying a large portion of that and most of

the left ventricle including the apex. Cross, Spalteholz, Le Count and others have shown that there is great variation in the anastomoses between the terminal branches of the two main coronary arteries.

The idea formerly held that the arteries are end-arteries is only true up to a certain point. Sudden blocking of the anterior descending branch of the left coronary artery, for example, produces changes which seem to show that there are no anastomoses. Gradual occlusion of the same artery, however, leads to no recognizable change during life, showing that the element of time enters into the question whether the finer branches join with each other or not. An exceedingly important point for the determination of the site of thrombosis or embolism is the anatomical narrowing of the anterior descending branch almost immediately after the main artery bifurcates. It is at this point, a typical site of predilection, where the greatest majority of occlusions take place.

Etiology.—The cause of this condition is the cause of local atheromatosis. Until we know what that is, we cannot say just what the cause of the lesion is. Wearn, Levine, White and others have shown that syphilis plays a very minor part in the causation. Occupation and sex are only determining factors. Chronic hypertension is found in many cases. The majority of the cases occur in the decade between 50–60 years, although an occasional case is seen in the late thirties, and Vaquez and others have reported upon cases in young men in the early twenties. These cases, however, are exceedingly rare. Alcohol, tobacco, exercise and food seem to have very little influence upon the causation of the disease. When we look at the situation, then, it is found that age is the only element which is constant, sex being next, with males predominating over females. Social status, thought by Osler and others to be a factor, can no longer be said to have any marked influence, as cases are found in the lower strata of society as well as in the upper classes.

Symptomatology.—Pathologists have noted for years the end-results of thrombosis of the coronary arteries, but it has been only within the past few years that the symptomatology of the condition has been worked out, so that today it is possible to diagnose with a very great degree of accuracy when this condition occurs during life. A typical case would be somewhat as follows:

A man in the prime of life between fifty and sixty years of age who had never had any serious illness and who had always enjoyed good health, in fact, he may have been of the sort who boasted about his health, would find that he had occasional pains over his heart. These pains would be more than a mere discomfort. They might be stabbing or gripping or burning in character. They are usually situated beneath the sternum and sometimes near the ensiform cartilage. Often the diagnosis of indigestion is made and the man himself thinks that he has indigestion. These pains may not give the individual any distress and they may not interfere in any way with his daily life, or they may gradually get more severe and he begins to notice that he is more short of breath on exertion than he used to be. Suddenly while sitting quietly, or in bed at night, he is seized with such a sudden agonizing pain that he often cannot stay quiet but restlessly moves around trying in various ways to ease the pain. If he has had severe pain before, he knows at once that this is something quite different than anything he had ever had before. He often gasps for breath, he breaks out into a cold clammy perspiration and he becomes slightly cyanosed. He is often nauseated and occasionally vomits. The pain may extend over the whole chest, down the left arm and even to the tips of the fingers, and may occasionally be felt in the right arm. The pain does not go away. Nothing that he can do seems to ease it in any way. It may last for hours or even two or three days with periods of ebb and flow of the violence of the pain.

Such is a typical history of sudden occlusion of a large branch. There are naturally certain variations in symptomatology. The patient may not be greatly cyanosed, he may not show much dyspnea, but he may be so weak that it is an effort for him to lift his hand. He feels as if at any minute he were going to die. Other symptoms frequently noted are nausea, vomiting, and diarrhea. Occasionally there is suppression of urine. There is an important group of

cases in which there is no pain. The initial symptom is sudden, distressing dyspnea followed by profound weakness. Often there is nausea. Hamman has grouped the symptoms and signs together in a very concise table.

1. The immediate symptoms associated with the occlusion; the original seizure.
 - A. Pain.
 - B. Shock.
 1. Prostration.
 2. Fall in blood pressure.
 3. Suppression of urine.
2. The symptoms associated with the myocardial damage, myocardial insufficiency.
 - A. Dyspnea.
 - B. Passive congestion.
 1. Cyanosis.
 2. Pulmonary edema.
 3. Enlarged liver.
 4. Albuminuria.
 5. Subcutaneous edema.
 - C. Cheyne-Stokes breathing.
 - D. Feeble cardiac impulse, faint heart sounds, gallop rhythm, murmurs, cardiac arrhythmias.
3. The symptoms associated with the myocardial infarct.
 - A. Fever and leukocytosis.
 - B. Pericarditis.
 - C. Embolic phenomena.
 - D. Cardiac aneurysm and rupture.
4. Additional symptoms.
 - A. Nausea, vomiting, diarrhea.
 - B. Facies.
 - C. Vasomotor symptoms.
 - D. Nervous symptoms.

Diagnosis.—PHYSICAL SIGNS.—The most striking fact about these cases is that the physical signs are not at all in proportion to the desperately ill appearance of the patients. On inspection one sees the peculiar ashen gray appearance of the face and skin caused by a mixture of cyanosis and pallor. The skin is most frequently cold and often beads of sweat are seen. In fact, the sweating may be so severe that the patient may need to have his night clothes changed every hour or two. The pulse may be of any nature. Usually it is irregular, often it is very rapid and thready, and occasionally it is fairly regular with numerous dropped beats, or in some cases it may be perfectly regular and of normal rate. The blood pressure is usually low but it may not be affected at all. In those cases where hypertension was known to have been present, a decrease in the systolic pressure without a corresponding decrease in the diastolic pressure is an indication of the weakness of the heart.

"Upon examining the heart the conspicuous, the impressive feature that at once attracts attention is the remarkable contrast between the symptoms of the myocardial insufficiency that have been observed and the entire lack of local manifestations of cardiac disease. For, as a rule, when the heart fails it is already hypertrophied from years of increased labors, and diffuse pulsations proclaim violent though ineffectual beating. In coronary occlusion we turn from beholding dyspnea, cyanosis, collapse to look upon the chest and are startled to see there no signs of tumult or of effort. Indeed, the throbbing usually present in health may be absent. We search for the apex beat with eye and finger and do not find it. We listen and the heart sounds come to the ear faintly as though from a great distance. Even the area of cardiac dullness may not be enlarged. These unaccustomed circumstances may mislead one

to detach attention from the heart, and if epigastric pain, distention and nausea be present, to fasten it upon the abdomen."

Fever is often present on the second or third day and may be as high as 102° F. There is usually a slight leukocytosis of the polymorphonuclear type, from 12,000 to 15,000 white cells, with rarely 20,000. This is readily understood when one bears in mind that the pathological process attracts large numbers of leukocytes. Should the softening reach the surface of the heart there is serous membrane irritation with fibrin formation and an audible friction rub. However, the friction rub is heard only in a very small percentage of cases. If it is present it practically settles the diagnosis, but its absence is no sign that widespread infarction has not taken place. It may be present only for a few days.

The lungs very early show mucous râles in the bases posteriorly. There is no change on percussion and the vocal fremitus may be slightly increased at the bases.

There are cases described where there are practically all the symptoms of coronary thrombosis, including the evident cardiac weakness, but in which there is practically *no pain*. Such cases undoubtedly exist, but they are certainly not common. Pain is by all odds the one outstanding symptom of occlusion of the coronary artery. All cases unfortunately do not recover, and one may divide the cases on the whole into three groups: those who die immediately, those who survive a few hours or days, and those who live for several years with some limitation of their former activities. Coronary thrombosis is the one primary cause of sudden dramatic death in an apparently healthy individual.

Certain of the cases naturally do not conform to the classical types. There may be the pain with only the profound weakness and cold clammy sweating. The cyanosis is not marked and the dyspnea is not noticeable. The weakness of the patient is out of all proportion to the physical signs. As a rule, in these cases the pulse rate is rapid. It is very small and the heart sounds are faint.

Another group of cases is accompanied by nausea, and even fainting.

ELECTROCARDIOGRAPHIC CHANGES.—The studies of F. M. Smith and others have shown that experimental sudden tying of the large branches of the coronary artery produces in the dogs who survive the operation, certain changes in the electrocardiogram. The changes consist of negativity of the T wave in all three leads and decrease in size of the QRS complex. These changes have been frequently confirmed and are diagnostic of coronary thrombosis. Herrick in 1912 was able to diagnose a case, confirmed at autopsy, after the study of such an electrocardiogram obtained from one of his patients. Pardee has called attention further to another interesting anomaly, namely, the immediate origin of the T wave from the descending limb of the R wave.

Barnes and Whiffen have produced evidence to show that it is possible in most cases to diagnose the seat of the occlusion, whether left or right artery, by the form of the electrocardiogram. Negative T waves in leads I and II are evidence of occlusion of the anterior descending branch of the left artery. Negative T waves in leads II and III are evidence of occlusion of the right coronary artery. In all studies the left coronary is more often occluded than the right, the proportion being from 3:1 to 2:1.

Unfortunately, even if it were possible to take an electrocardiogram of every patient with coronary thrombosis, these characteristic changes do not always appear. If an electrocardiogram shows such changes, diagnosis is certain. However, if in a suspected case the electrocardiogram shows none of these characteristic changes, it does not mean that coronary thrombosis has not taken place. These electrocardiographic changes are valuable only if they are positive.

DIFFERENTIAL DIAGNOSIS.—The most important diseases to be differentiated from coronary thrombosis are: (a) *Angina Pectoris*.—The typical angina pectoris of effort occurs at practically the same age group. The pain is violent, agonizing, vise-like and there is the fear of impending death. The patient

stops in his tracks, leans up against some place for support, but there is no dyspnea, there is no cyanosis; on the contrary, pallor is the rule, the blood pressure often rises and the attack is over in a few minutes. Inhalation of amyl nitrite or the placing of a tablet of one one-hundredth grain of nitroglycerin under the tongue readily stops the attack. The patient can then go on about his business. Any increased effort precipitates another attack. Not infrequently the attacks of coronary thrombosis are preceded by several years of angina pectoris. The change is recognized by the fact that the attacks last longer, are accompanied by shortness of breath and are not brought on by effort. In the angina pectoris of effort the onset of heart failure causes cessation of pain. In thrombosis of the coronary arteries an attack may come on while the patient is in bed with signs of heart failure.

(b) *Valvular Heart Disease*.—Certain cases of mitral stenosis occasionally suffer with rather sharp attacks of precordial pain. However, the age of the patient is usually less than that in coronary thrombosis and the examination of the heart should at once settle the diagnosis of the cardiac lesion. There should be no great difficulty in distinguishing the pain of valvular heart disease from that of coronary thrombosis unless the latter occurs in a person who has valvular heart disease. This, however, seems to be a comparatively unusual occurrence.

(c) *Syphilitic Aortitis*.—Cases of paroxysmal pain in syphilitic aortitis which have been described in the literature lead one to believe that possibly the authors were describing cases of coronary thrombosis. The pain in syphilitic aortitis is usually situated directly beneath the manubrium. It is an ache or an oppression rather than a stabbing, agonizing pain and, as a rule, does not spread towards the arm. The infrequency of syphilis in all the reported cases of coronary thrombosis (White, among others, one out of 62 cases) is rather striking in view of the fact that syphilis attacks the arch of the aorta and narrows the openings of the coronary arteries.

(d) *Acute Abdominal Accidents*.—Occasionally the differential diagnosis between coronary thrombosis and acute abdominal conditions in the upper part of the abdomen may be exceedingly difficult. It is well to bear in mind that there is this similarity of symptoms. When the pain in coronary thrombosis is at the tip of the ensiform, when there is nausea, vomiting, rigidity of the abdomen and collapse with rapid small pulse, it is readily seen that the diagnosis between these two such different diseases may be quite difficult. Levine and Tranter saw two cases, one of which was operated upon and died upon the operating table; the other was about to be operated on but it was thought best to wait, and the patient died the following day. Autopsy in both cases showed no abdominal lesions but thrombosis of the descending branch of the left coronary artery. Differentiation has to be made from perforation of a duodenal ulcer, perforation of a gastric ulcer, an acute attack of gallstone disease, perforation of the gallbladder and acute pancreatitis. A careful history is of great importance. Previous attacks of pain with shortness of breath should put one on one's guard. All the conditions mentioned above with rare exceptions have shown some symptoms previous to the acute attack. There are cases of sudden perforation of a gastric ulcer in which there has been no previous gastric complaint, but they are not common.

On physical examination the similarity may be striking, the board-like hardness of the abdomen, the spasm, even tenderness may all be present in the region above the navel. The condition of the heart gives practically no assistance in the diagnosis. The important differential diagnostic feature is the examination with the stethoscope of the bases of the lungs posteriorly. It is rare in such a violent attack of coronary thrombosis not to find râles in the bases of the lungs. The sudden occlusion of the artery so disturbs the circulation of the left heart that edema of the lungs sets in very quickly.

Effects of Thrombosis on the Heart.—Sudden occlusion of a coronary artery profoundly affects the function of the heart. The majority of cases occur in the left ventricle. This chamber at once becomes unable to carry the load. The blood pressure usually falls and blood which is coming from the right side

of the heart through the lungs becomes dammed back upon the lesser circulation and pulmonary edema results. Some of the cases of acute pulmonary edema are very probably the result of coronary thrombosis. The rhythm of the heart may be profoundly disturbed and the heart may at once show the signs of congestive failure. It is important to remember that heart failure may be accompanied by a perfectly normal regular rhythm, so that when one finds a heart beating regularly and practically at the normal rate, one may not realize that the heart nevertheless is failing. Parkinson and Clark-Kennedy have studied this question and have concluded that the prognosis in failure with regular rhythm is less favorable than in the corresponding degree of failure with auricular fibrillation.

As a result of sudden blocking of the descending branch of the anterior coronary artery, the apex of the left ventricle is deprived of its blood supply and rapid softening of the muscle takes place. Under such conditions one of three things may happen: (1) Profound symptoms of thrombosis of the coronary artery with eventual scar tissue and thinning of the apex, (2) aneurysm of the apex, (3) rupture of the heart with extravasation of blood into the pericardium, resulting in sudden death. That such accidents occur is well known to all pathologists. Fortunately they are not common. Krumbhaar and Crowell have studied 22 cases and have collected 632 from the literature. There were 7 cases among 16,000 autopsies at the Philadelphia General Hospital. Males predominated, 304 to 217. The majority of the cases occurred in the decade 60-70. Syphilis, which is by far the commonest cause of aortic aneurysm, was rare except in cases under 40 years of age. The exciting causes were numerous. Twenty-one died during sleep, showing that exercise plays no part in the etiology. The apex of the left ventricle was the site in the great majority of spontaneous cases, although there were ruptures of other cavities. A small number could be accounted for by acute and chronic infectious processes. A few were due to traumatism. *In every spontaneous rupture there was disease of the coronary arteries leading to thrombosis.*

The early symptoms are like those of coronary disease. Death is usually sudden. The terminal symptoms are acute collapse, air hunger, pallor or deep cyanosis, stertorous breathing, cold sweats, sometimes vomiting, convulsions or unconsciousness. Rare cases survive the initial rupture several hours and show signs of rapid heart failure.

Still another result of coronary thrombosis is aneurysm of the heart. This is usually found at the apex and is the result of the distribution of blood from the anterior descending branch of the left artery, which when occluded deprives the apex of its blood supply and causes acute softening of the muscle. Aneurysms of the heart are not diagnosable. They are apt to rupture, producing then the same symptoms as in any case of rupture of the heart.

After a man has had an attack of coronary thrombosis, his heart is never as strong as it was before the attack. While he may live for several years in comparative comfort, the level at which he lives his life is much lower than normal. He is subject to further attacks in one of which he may suddenly die, and there is no foretelling whether or not he is going to have another attack.

It is surprising how much damage can be done to the coronary circulation without apparently limiting the individual's activities.

The author saw a case of a recruit aged 42, who was passed for military service. Three days later he suddenly pitched forward on the floor of the Post Office and died instantly. At autopsy the right coronary artery was a fibrous cord. The left was the seat of extensive atheromatous changes which so narrowed the descending limb of the anterior artery that it scarcely admitted an ordinary pin. At the narrowest point, and corresponding to a small atheromatous ulcer, there was a fresh thrombus completely occluding the artery.

Smith and Grober report a case of coronary thrombosis in a heart in which there was congenital absence of the left coronary artery. The patient was 46 years old, a laborer. There was a large single right artery with branches from it taking the place of the anterior branch of the left artery. An interesting and

important feature was the absence of aortic sclerosis with extensive senile atherosclerotic changes in the coronary arteries.

The heart apparently can obtain its blood supply for a short time at any rate from the thebesian vessels (Wearn) or from the cavities themselves.

Wearn told the author of a heart of a middle-aged colored woman in which both coronary openings were sealed off. She died suddenly but must have lived some time deriving the blood supply of her heart probably through the ventricular walls. Such anomalous conditions are on the whole rather rare. The variations in the anastomosis of the coronary vessels are very great. The subject had been studied especially by Oberhelman and Le Count. The variations in the anastomosis account for the great difference in symptoms in those who suffer from a coronary thrombosis. What might kill one might only cause temporary disability to another.

Clinical Varieties.—For convenience of description, and as a useful working basis, Herrick divides the cases into four groups:

(1) This group consists of cases of instantaneous death in which there is no death struggle, the heart beat and breathing stopping at once.

(2) To this group belong cases in which death results within a few minutes or a few hours after the obstruction occurs. These are the patients who are found dead, or who are clearly in the death agony, when the physician arrives after a hasty warning.

(3) This group includes cases of severity in which, however, death is delayed for several hours, days, or months, and in which recovery even occurs.

(4) This group is one which may only be assumed to exist, and embraces cases with mild symptoms, for example, a slight precordial pain, ordinarily not recognized, due to obstruction in the smallest branches of the arteries.

Treatment.—When one is called to see a case and diagnoses coronary thrombosis, the only drug which is of any value whatsoever is **morphine in full doses**. The author does not hesitate to give **one-half grain hypodermically**, repeating it in one-half hour if necessary. When one takes into consideration the damage done to the heart, **nitroglycerin** would appear to be **contraindicated**. It is probably **not wise to begin digitalis in full doses until the heart has somewhat rallied** after its first profound shock. The digitalis can be given in full doses according to Eggleston or some modification of the method. The important point is to **digitalize the patient as quickly as possible**. Following that, one can give doses of digitalis, 1 cc. of the tincture, for example, once or twice a day over a period of several weeks. Occasionally, as in a case of ventricular tachycardia reported by Levine and in a similar case recently seen by the author, **quinidine sulphate** has a life-saving effect. Levine gave his patient enormous doses, 1 gm. (15 grains) every four hours for six doses. It was only under such massive doses that the heart rate returned to normal. In my case 0.6 gm. (10 grains) in a single dose brought an apparently dying man back to life and a heart rate of over 200 to one of 76 within three hours. It is well to bear quinidine in mind. The dose is variable and the patient should be closely watched. There is not the danger in its administration in such cases, the result of coronary thrombosis, as there probably is in cases of old fibrillating hearts. Drugs, however, are the least important part of the treatment.

The most important of all measures is **prolonged bed rest**. It is not possible to say how long the patient should be kept in bed. This depends somewhat upon the character of the heart and upon the severity of the attack, as well as upon the signs of cardiac failure. A safe period of time is **not less than six weeks** and the time may vary all the way from that up to six months. Every practitioner must be guided by his own judgment. The important point to remember is that it is better to keep a case in bed a week too long than to let him get up a week too soon. The **diet** should be light and easily digested, enough **water** should be given to **keep the kidneys** acting normally, attention should be paid to the daily bowel movement. The **milder laxatives** or soap-sud enemata are preferable. There is no kind of food which the patient should be deprived of, providing he wishes the food. It is much more important to see

that the quantity is kept within limits than it is to deprive a man of meat or eggs or some other protein which is thought to be harmful but which in fact is not harmful.

The patient should be allowed to get up very gradually at the end of the bed-rest period. He should first sit up in bed for a few days, then a half an hour in a chair, then an hour, and so gradually until after ten days or two weeks he will begin to walk around the room. Too much emphasis can not be laid upon the care with which these invalids are handled.

Prognosis.—It is very difficult to give a prognosis in cases of coronary thrombosis. One not infrequently sees hearts at autopsy in which there has evidently been an enormous necrotic area which has completely healed, leaving only a portion of the septum and converting the apex into a tough membrane. The patients in whom these old lesions are found, died of some other disease than heart disease. The longest case that the author is personally aware of is six years. This particular patient was seen in the latter part of 1926 suffering from another attack. It seemed probable that he would survive this latter attack. He died of heart failure two weeks after he was seen. So much depends upon the ability of the remaining blood vessels to produce anastomoses quickly that a complete occlusion of the descending branch, which in one individual would be followed by sudden death, in another, would produce only a serious attack with recovery. White analyzed 62 of his own cases and reviewed the literature including the cases of Sir James MacKenzie. His conclusions are as follows:

"It may be said, in the first place, that patients often survive for years in good or in fair condition. In fact, the average duration of life after the attack in this group of sixty-two patients, half of whom are still alive, is close to two years. The sex and age at which the attack occurs seem to make little or no difference so far as prognosis is concerned. Hypertension, evident sclerosis and syphilis alter the prognosis hardly at all. Syphilis is rare in either group. The heart is enlarged in the majority of patients of both living and dead groups. Poor heart sounds and congestive failure do, however, add to the gravity of the prognosis. The finding of fever or paroxysmal auricular fibrillation at the time of the attack of coronary thrombosis has made no difference in prognosis in the few cases tabulated here.

"Pericarditis was somewhat more frequent in the patients who died. The electrocardiogram did not help, though the very slow pulse of complete heart block was a bad sign. It happened that intraventricular block was more common in the survivors. Neither the previous occurrence of angina pectoris nor its duration prior to the attack of coronary thrombosis has seemed to matter."

Pathology.—The pathological change which almost invariably accompanies thrombosis or embolism is atheromatosis of the coronary arteries. The fact that there is an anatomical narrowing of the anterior descending branch of the left artery makes this spot the site where most of the occlusions take place. Atheromatosis with calcification at this point produces greater interference with blood supply than would the same amount of atheromatosis in any adjacent part of the artery.

The heart receives the greatest part of its blood in diastole, and F. M. Smith and his coworkers have demonstrated that the coronary flow is more dependent upon the height of the diastolic pressure than upon the height of the systolic pressure.

The immediate result of a sudden occlusion of a large branch is anemic necrosis, myomalacia. The part is first pale, then becomes soft, soon is surrounded by a hemorrhagic zone with leukocytes, the softened anemic area is gradually infiltrated with leukocytes and fibroblasts and the end-result is complete loss of muscle with a scar. Should this occur at the apex, the usually thickened muscular apex may be reduced to a thin tough membrane lined on the inside by endocardium, on the outside by epicardium, between which two endothelial layers is fibrous tissue.

It is now generally conceded that the arteries of the heart are not terminal arteries. There is more or less anastomosis among the terminal branches of the

two coronary arteries. There seems to be individual variation, some men apparently having more anastomosis than others. This is certainly true of animals. The vessels of Thebesius, also must be considered in the anastomosis. Consequently, a slow occlusion of even a large branch of one artery is not incompatible with good health and considerable bodily activity, as was illustrated in the above case which the author saw during life and at autopsy.

Experimentally, the ligation of a large branch of an artery is followed by acute softening of the part supplied by the occluded vessel. Upon the pericardial surface, this occasions inflammation, which results in fibrinous deposit and physical evidences of friction. Even if no arteriosclerosis is present in the arteries of the body, the coronary arteries generally reveal lesions of arteriosclerosis of the nodular type. The area of necrosis, following the obstruction of one of the large branches of a coronary artery, varies somewhat in extent, depending upon the number of anastomosing channels and upon the size of the artery. Externally, there is a more or less triangular depressed area, the base usually lying toward the apex of the heart. The area is pale in color and is soft or firm, depending upon the age of the lesion. In the experimental animals, there is "often an area occupying the apex that is of soft consistency, regardless of the age of the lesion and of the amount of fibrosis in the surrounding tissue" (Smith). At the apex there is often extensive softening, in which the muscle is reduced to the thinness of paper. The degeneration is greatest on the endocardial surface. The papillary muscles also become softened and pinched off at the apices.

In dogs, the most constant lesions are those resulting from ligation of the ramus circumflex sinister. "The ligation of the first descending branch of this artery generally resulted in fibrosis of the anterior papillary muscle; the ligation of the posterior descending portion of the left circumflex artery resulted in fibrosis of the posterior papillary muscle" (Smith). Microscopically, the early lesions show pale staining of the muscle fibers and nuclei, and infiltration with round cells and red blood cells. Later fibrous tissue cells are found, and the muscle cells show advanced degeneration, until finally the whole area is replaced by scar tissue.

PERIARTERITIS NODOSA

Definition.—This is a rare and acute disease, which is characterized by pains in the muscles or joints, by fever, by leukocytosis, and by small aneurysmal dilations on many of the smaller arteries. It leads almost invariably to a fatal outcome.

Etiology.—The cause of the disease is not absolutely determined. According to Lamb, there have been three main views:

(1) The syphilitic, which is now rejected by most authors. There have been no serological data to support it. Further, it is of interest that a similar disease is found in stags.

(2) The mechanical, which is only of historical interest. It was thought that high blood pressure ruptured the media, which was later further injured by some toxic substance.

(3) The infectious or toxic view. This is the one now most commonly held. The organisms of the streptococcus group are thought to be responsible for the lesions. Some have thought that the *Streptococcus viridans*, specifically, is the one most often concerned. Others believe that any virulent streptococcus may cause the peculiar nodular lesions in the small arteries. The results of injections into animals have been uniformly negative, although Klotz claims to have produced perivascular lesions with *Streptococcus mitis* and *Streptococcus salivarius* in the arteries of rabbits. These lesions were inflammatory in type and had some slight resemblance to the lesions of human periarteritis nodosa.

Klotz collected 42 cases up to 1918. The youngest patient was two and one-half months, the oldest was fifty-seven years old. Males are affected more often than females, the proportion being 3 to 1. The condition seems to be most frequent in adolescence and early adult life. There are no predisposing causes.

Symptomatology.—There is nothing definite in the onset or cause of the disease which enables a diagnosis to be made with reasonable certainty. The onset may be acute or gradual. The development of symptoms is similar to that of almost any infection. There are pains in the muscles or in the joints. At times there is abdominal pain. Fever is usually present. There is weakness, prostration, and occasionally disturbance of sensation. In 61 per cent of Klotz's cases there was edema of the ankles. The blood shows a leukocytosis of the polynuclear type. The urine may or may not contain albumin. The diagnostic criterion is the discovery of small nodules along the course of small arteries. These were present in only 8 of Klotz's cases.

Diagnosis.—This is usually quite impossible unless there are the characteristic nodules on the arteries. There are no laboratory findings, and the data from blood cultures would not establish the diagnosis of the specific malady. Final diagnosis is made only on the autopsy table, and even then it may not be accurately made on account of the small number of arterioles which may be affected. The microscopical picture establishes the diagnosis.

Treatment.—In a disease so difficult to diagnose, the treatment must of necessity be entirely symptomatic. Supporting measures are indicated. **Water** should be freely urged upon the patient. The **diet** should be **light**, with a preference for carbohydrates and fats. Fever is no contra-indication to food provided the patient has an appetite.

Prognosis.—The prognosis is grave, if the diagnosis can be made during life. There is actually no opportunity for prognosis until diagnosis is made. Since this is practically impossible, prognosis must depend upon a careful valuation of all the symptoms, together with the course of the disease. The disease may last from one to several weeks.

Pathology.—The process is one essentially affecting the small arteries, more particularly those of the kidney, stomach, mesentery, liver and heart, and occasionally of the skin, thyroid, lungs, brain and spleen. The aorta and large branches show no involvement microscopically.

Klotz believes that the lesions of periarteritis nodosa differ from the common periarterial inflammations only in the peculiar manner of damage to the arterial wall. The distribution and the progress of the disease along particular branches of arteries is not unique for this lesion. Microscopical examination reveals a nonsuppurative inflammatory process beginning in the adventitia. More acute inflammation reveals polymorphonuclear leukocytes, and later eosinophils are often found. The process extends along the lymphatics of the vasa vasorum to the outer coat of the media, where, at times, widespread degeneration occurs. The weakening of the wall produces small aneurysmal dilatations which frequently clot, and thrombosis of the vessel results. The aneurysm is acute, that is, the clot is not laminated and cannot be differentiated from the inflammation in the vessel proper, inasmuch as the one merges into the other. The degeneration of the media is hyaline in character. It seems partly nutritional and partly toxic. In no case is the whole circumference of the vessel affected.

CLINICAL BLOOD PRESSURE

Definition.—Blood pressure may be defined as the force which is exerted by the heart beat. It is measured, usually, in the brachial artery by means of an instrument which records in millimeters the force which raises a column of mercury above the zero point on a graduated scale.

Three figures in blood pressure are recorded: (1) the maximal or systolic pressure, (2) the minimal or diastolic pressure, and (3) the difference between the two, the pulse pressure. These constitute the blood pressure picture and are usually written thus: 120—80—40. This means that 120 mm. Hg is the systolic pressure, 80 mm. Hg is the diastolic pressure, and 40 mm. Hg is the pulse pressure. The three figures should in all cases be given. To this should be added the pulse rate. The product of pulse pressure times pulse rate (P.P. x P.R.)

equals volume output per unit of time. This formula, according to Erlanger, is correct for most cases, but it does not obtain under every condition.

Mean pressure is the average pressure at a given point, but it is not the arithmetical mean of the systolic and diastolic pressures. The mean pressure lies nearer to the diastolic pressure than to the systolic pressure.

Technic of Blood Pressure Measurements.—Various types of instruments have been used to measure the blood pressure. Some are made with straight columns of mercury, some with a U-tube containing mercury, and some are made with a dial in which the expansion of thin plates of metal causes a hand to move around a central fixed point. The dial instruments are at present most frequently used. Much has been written about the relative merits of the mercury *versus* the dial instrument. At present it seems to be generally conceded that, for all purposes of blood pressure estimation, the mercury instrument has no particular advantage in accuracy over the dial instrument. The dial is much more convenient. In fact, there is no absolute accuracy in any clinical blood pressure instrument. The pressure in the brachial artery approximates, but does not equal, that in the left ventricle, and the pressure is subject to sudden fluctuations. The mistake has been made of paying too much attention to the blood pressure reading alone. The public has become aware of the fact that life insurance companies refuse applicants with a blood pressure above a certain point, and it has concluded that blood pressure is a very important index to health. Importance, far out of proportion to their value, has thus been forced upon blood pressure estimations. It is time that a saner view of the actual value of blood pressure estimations should prevail.

The arm band, which must be 12 cm. wide, is snugly, not tightly, wrapped around the upper arm so that the lower edge of the arm band is from 2 to 3 cm. above the bend of the elbow. The patient should be sitting in a comfortable, relaxed position with the arm resting on a table; or he should be lying down with arm comfortably outstretched on the bed. The air bulb is then rapidly compressed so that the pulse at the wrist is obliterated. By means of the escape valve, the air is gradually released so that the pressure in the arm band falls. Systolic pressure is reached when the pressure above the compressed artery is just sufficient to force blood through it. It may be determined by palpating the radial and feeling the first pulse wave, or preferably, by listening with the bell of the stethoscope over the artery at the bend of the elbow. The latter method, known as the auscultatory method, is the more accurate and the one more frequently used. As the pressure is reduced, five phases are differentiated as follows:

The first is a sharp, distinct click. This is the time to read systolic pressure. Then follows a murmur with the click or a murmur alone, the second phase. The third phase is ushered in by a loud snappy sound. This suddenly yields to a dull tone, the fourth phase. At this point, when the loud third tone suddenly becomes dull, the diastolic pressure is read. This dull tone fades away into absence of sound, the fifth phase. In the normal person all these tones are readily heard.

In some cases of high blood pressure the second phase murmur may suddenly cease, or it may be so feeble as to be scarcely heard. As the pressure is further reduced, the intensely loud third tone is followed by the fourth. Attention is called to this phenomenon, as neglect to bear this in mind may lead to error.

Certain ordinary precautions must be used in order to obtain reliable results. The cuff should be warm, and should be wrapped around the bare arm. When using the stethoscope, the bell should be placed firmly, but it should not press too hard on the arm. The artery must bisect the circle of the bell. Care must be exercised so that the edge of the bell is not tilted; this might compress the artery above or below the center of the bell. This faulty technic may produce tones which may occasion considerable error in the estimation.

It is generally agreed that the first sound, first phase, represents the systolic pressure. The author and others believe that the fourth phase is the point at which the diastolic pressure should be read. Some believe that the cessation of all sound is the diastolic point. Except in most high pressure cases, and in a few normal cases, the difference between these two points amounts only to 4 to 6 mm. Practically, it makes little difference which method is employed, provided one or the other is always used.

Mechanism of Maintenance of Blood Pressure.—The maintenance of the blood pressure depends upon the pumping action of the left ventricle and the resistance offered to the flow of blood in the arterioles and capillaries throughout the body. This resistance is known as the peripheral resistance and is equal to the diastolic pressure. This force is exerted on the aortic side of the aortic valves during diastole and, therefore, represents the amount of dead weight lifted by the heart muscle in order to open the aortic valves. The diastolic pressure always measures the force expended by the left ventricle to overcome the back pressure exerted by the peripheral resistance. The actual driving-force which sends the blood to the periphery is the pulse pressure. The large arteries act as distributing channels and the aorta especially acts as an elastic reservoir, which expands at each influx of blood during systole and contracts on the column of blood during diastole. The driving-force during diastole is, therefore, the elastic rebound of the aorta. Changes in peripheral resistance are due to contractions of large areas of small arterioles or capillaries. Contraction of capillaries may be so extensive as to block off a large area and cause greatly increased peripheral resistance.

A further important factor is the venous flow. For the circulation to be in equilibrium, as much blood must enter the heart from the systemic veins during diastole as is discharged by the left ventricle during systole. In order that this may always occur, there must be an unobstructed venous return flow. Venous pressure must always be low. A rise of pressure on the venous side, due to engorgement, usually leads to a rise in diastolic pressure, and may lead at the same time to a fall of systolic pressure. The embarrassment of the circulation under such conditions is great, and the heart may not be able to respond with enough force to raise the systolic pressure.

VASOMOTOR SYSTEM.—Although the driving-force is exerted by the heart, aided by the active elasticity of the great vessels, there would be no continuous circulation unless there were some resistance against which the heart could pump. The control of the arterioles and probably of the capillaries by the vasomotor system supplies the contractile tonus which makes possible the maintenance of the circulation. Probably the most important vasomotor area in the body is the splanchnic area. The arterioles and capillaries of this great area are capable of containing all the blood in the body, and in certain conditions a loss of vasomotor tone in this area causes bleeding into one's own vessels.

Pressure on the abdomen may cause a definite rise in systolic pressure. The vasomotor system is composed of two sets of fibers, vasoconstrictor and vasodilator fibers.

The vasoconstrictor fibers have a bilateral center in the medulla which is always in a state of tone. Under certain conditions it undergoes rhythmical fluctuations known as Traube waves. "The axons leading from these medullary cells pass down the cord to terminate around cells of the anterior horn from the upper thoracic level to the upper lumbar, and constitute, with the medullary cell, the first neuron. The axons of the anterior horn cells are medullated and constitute the second neuron in the chain, the so-called preganglionic fibers. They pass from the cord in the white rami communicantes from the first thoracic to the second or fourth lumbar segments, and, entering the sympathetic chain, have one of three destinations. Those destined for the extremities end around cells in the sympathetic chain. The nonmedullated fibers of these sympathetic cells constitute the third neuron, the postganglionic fibers. They pass by the gray rami communicantes back to the spinal cord and thence accompany the appropriate spinal nerves to their destination. The preganglionic fibers destined

for the deeper vessels of the head pass through the white rami of the first to sixth thoracic segments and up the sympathetic to the superior cervical ganglion. From this point the associated postganglionic fibers are distributed through the carotid and other vascular plexus. The preganglionic fibers destined for the vessels of the abdominal and pelvic viscera pass directly through the sympathetic chain and by way of the splanchnic nerves to the celiac, inferior mesenteric, or other large prevertebral ganglia. From these ganglia the postganglionic fibers are distributed to the plexus around the abdominal vessels" (Norris). Pressor afferent fibers must end around the medullary center, bringing stimuli which lead to heightened tone and increased constriction of large areas. Also depressor fibers, which act to relax the tone, end around the center and cause dilatation of small or large areas.

Although there have been no vasoconstrictor fibers demonstrated in the vessels of the brain, there must be fibers which pass from the brain to the medullary vasomotor center. Mental work and mental strain produce an elevation of pressure by causing general systemic vasoconstriction.*

The vasodilator fibers are scattered throughout various nerves, for example, in the cervical sympathetic nerve, the chorda tympani, the fifth cranial nerve, the splanchnic nerves, etc. From the first to the third sacral segments of the cord, dilator fibers pass to the hypogastric plexus and become the nervi erigentes, which are distributed to the corpora cavernosa of the penis and clitoris.

There is no single center for the vasodilator fibers. Probably there is a series of local centers which control the organs. The dilator centers are not in continual tone as is the constrictor center. It is not known how the fibers act on the muscular walls of the vessels.

EFFECTS OF CHEMICAL SUBSTANCES.—Various chemical substances have been found experimentally to influence blood pressure. They may be inorganic salts, as barium chloride; they may be alkaloids, as nicotine; or they may be substances derived from glands of internal secretion, such as adrenaline and pituitrin. In spite of the general impression that adrenaline is found in the blood and elevates pressure, a mass of data is now accumulating which proves that adrenaline is found in any demonstrable quantity only in the adrenal vein.

The injection of extract of the infundibular portion of the pituitary gland will raise the blood pressure, but the effect is not prolonged. Various unknown substances resulting from vicarious metabolism must circulate in the blood stream and exert at times, or constantly, deleterious effects. If, as has been recently shown, the capillaries are contractile, such circulating substances could conceivably produce such widespread constriction as to lead to permanent changes in the blood vessel and heart. Whether or not hypertension is produced in this manner is not actually demonstrated, but what evidence there is at hand leads to the belief that such a mechanism is a cause of the hypertension.

RESPIRATORY EFFECTS.—All are familiar with the record of blood pressure taken with cannula in the carotid artery of a dog. Here are seen rhythmical fluctuations of the record due to the respiration, a slight rise on inspiration, and a slight fall on expiration. Ordinarily these fluctuations, also found in human beings, during quiet inspiration, are so slight as to be a negligible factor in pressure estimations. In dyspnea or deep stertorous breathing the systolic pressure may be difficult to register. With the arm band on and compressed, the point in the release of compression when the first tone is heard may vary at deep inspiration or forced expiration as much as 20 mm. Hg. Obviously both cannot be correct. The author's practice in such exceptional cases is to take the average as the systolic pressure. Frequent subsequent estimations will reveal the average pressure.

It cannot be too strongly emphasized that one blood pressure estimation has little or no significance unless it is made under rigid conditions and is absolutely

* While no direct vasomotor control of the cerebral arteries has been actually demonstrated, analogy would lead us to believe that there is the same system of nerve fibers, causing constriction and dilatation of the arteries of the brain, as is present in arteries of similar structure throughout the rest of the body. Some day they will be demonstrated.

within the limits of normal. Variations are so sudden that within a moment the pressure may show wide fluctuations. The respiratory mechanism assists in some of the fluctuations.

Average Normal Blood Pressure.—In healthy people there is an average normal blood pressure which may vary considerably but which tends always to assume the average for the age and sex of the person. Innumerable estimations have been made, so that a good idea of what constitutes the average at decade periods can now be obtained. The following table is taken from a series of published figures of blood pressure estimations:

TABLE 1. SYSTOLIC BLOOD PRESSURE

Age	High	Low	Average
15 to 30 years	142	104	123
30 to 40 "	145	107	126
40 to 50 "	147	110	128
50 to 60 "	150	117	133
60 to 70 "	156	121	138

The diastolic pressure is from 70 to 85 per cent of the systolic pressure. Faught considers that 120 mm. is the average systolic pressure for a man twenty years old. For every additional two years of age 1 mm. is added. This is a fair working rule, but it places the systolic pressure for a man of sixty years at the upper limit of 140 mm., a figure which seems too low.

Kilgore (*Lancet*, Aug. 24, 1918) considers that the normal systolic pressure given in textbooks is too high. Basing his figures on the examination of 500 students in the recumbent position, he found that quite a number were below 100, and an occasional one was as low as 85 or 90. He thinks that the systolic pressure should be retained as the most important measurement, and that palpation of the radial should be used instead of the auscultatory method.

It is seen that age has some effect on the blood pressure, although this is not by any means always the case. Many persons eighty years of age have 120—80—40 for a pressure picture. The figures above indicate only that it could not be considered abnormal if a man of sixty should have a systolic pressure of 150 mm. Hg.

The diastolic pressure is normally below 100 mm. Hg. Usually it is from 70 to 90 mm.; in most healthy men and women it approximates 80 mm. The pulse pressure is about 40 mm., but perfectly healthy persons are seen with a pulse pressure of only 30 mm. Women, as a rule, have a systolic pressure slightly lower than that of men. The diastolic pressure in women is about the same as that in men.

With variations in the systolic pressures of normal persons amounting to 30 or more millimeters of mercury, it is of no particular importance to spend time estimating the systolic pressure by a series of half a dozen readings. The important point is to know that the pressure falls within the average for the age period.

The first reading is usually the highest, especially if the patient has never before had his blood pressure measured. This should be discarded and the second reading taken. After some years' experience the writer has found that his average of three or four readings varies so slightly from any one reading after the second reading, that he has entirely discarded the method of taking the average of several readings. It is only in cases in which the persons are excited and the pressure at the upper limit that the average is sometimes taken. However, blood pressure is not an absolute constant from day to day, or from hour to hour. A variation in systolic pressure of 20 mm. is not abnormal.

The diastolic pressure is quite constant. That is to say, the variations at rest are rarely more than from 6 to 8 mm. As the diastolic pressure measures

the peripheral resistance and the force which the left ventricle uses in order to start the blood in circulation, it is a better index to cardiac work than is the systolic pressure. The writer feels that too little attention has been paid to this part of the blood pressure. Now, however, it is noticeable that all observers report the whole pressure picture and most physicians concede the importance of the diastolic pressure.

VARIATIONS IN BLOOD PRESSURE UNDER PHYSIOLOGICAL CONDITIONS.—That the blood pressure of any individual is not a constant, unchanging force is well known. Many conditions affect the blood pressure which cause marked fluctuations in the systolic pressure and which are perfectly compatible with normal hearts and normal vascular systems. Neglect to take into consideration the normal variability has led to error and to unnecessary mental anguish on the part of the patients. Some of the common variations are:

Diurnal.—Weyse and Lutz and others have shown that the blood pressure varies somewhat during the day and tends to rise towards evening. The systolic pressure only is affected. The diastolic pressure remains practically constant.

Sleep.—During sleep the blood pressure is the lowest for the twenty-four hours. As the early morning hours approach, the systolic pressure rises gradually. The pressure, when one wakes slowly and normally, is the lowest of any for the waking hours. The diastolic pressure is less affected than the systolic.

Posture.—There is a slight variation in the systolic pressure as one rises to a sitting or standing posture. It is highest in the standing position. On *a priori* grounds this would be expected. The difference is not great, usually not more than 10 mm. for the systolic pressure. The diastolic pressure usually rises slightly but not to the same degree.

Eating.—After a meal the systolic pressure always shows a slight, but appreciable rise. The pulse rate is slightly increased and the volume output is greater. The diastolic pressure, as a rule, does not rise. Within limits the greater the meal, the higher is the pressure.

Exercise.—Exercise in the normal person always causes a rise in pressure. The whole pressure picture rises, but the systolic rises faster and proportionately much higher than the diastolic pressure. A rise of from 30 to 40 mm. is not uncommon. The pulse pressure is much increased. The volume output is greater, for the pulse rate also rises and the product P.P. \times P.R. is increased.

Emotional States.—The blood pressure is greatly influenced by emotional states. Excitement, fear, apprehension of the physical examination, attention directed to the blood pressure, concentrated attention watching the estimation, all tend to raise the systolic pressure. It is, therefore, necessary always to allay fear and to attempt to place the patient in as calm and relaxed a state as possible, particularly at the first examination.

Menstruation.—There is a slight premenstrual rise, but as a rule it is not great, and when the flow is established the pressure returns to its usual height. Women who suffer with great premenstrual pain are apt to have a greater rise in blood pressure than those without pain.

PRESSURE IN THE DIFFERENT BRANCHES OF THE VASCULAR TREE.—At the heart the systolic pressure is greatest. As the branches come off from the aorta, the bed begins to widen until at the capillaries the arterial bed is at its widest and all pulse is lost. Only in states of great vasodilatation is the pulse transmitted as far as the capillaries. The most rapid fall in pressure occurs between the arterioles and the capillaries. The fall affects the systolic much more than the diastolic pressure, and finally the pulse pressure is reduced practically to zero, the systolic pressure equaling the peripheral resistance. Any increase in venous pressure reacts at once upon the capillary bed and raises the capillary pressure more than it would be raised by an increased systolic arterial pressure.

Approximately, the pressure in the vascular tree at various levels is shown in the following schema:

TABLE 2. BLOOD PRESSURE AT VARIOUS LEVELS

	Systolic	Diastolic
Left ventricle	150	
Aorta	150	100
Brachial artery	120	80
Radial artery	100	70
Arterioles	80	60
Capillaries	20	20
Small veins	20	20
Femoral vein	20	
Inferior vena cava	3	

This schema lays no claim to accuracy; it shows only the general idea of decrease in pressure at the various levels.

In the recumbent position, the lateral pressure throughout the whole aorta is about the same. It has been shown, as would be expected, that the pressure in the femorals is greater than that in the brachials.

In the erect posture, the variations are greater because of the weight of the column of blood. The venous pressure is largely dependent upon the height of the column of blood above or below the level of the heart. Hence, for example, the pressure in the leg veins is greater than that in the arm veins. The veins are usually fuller in the lower extremities than in the upper.

Venous Pressure.—This has been a much neglected phase of blood pressure. In the opinion of many men it is of more importance under certain conditions than is the arterial pressure. A simple and satisfactory, but rough, estimation of the venous pressure is secured by raising the hand above the level of the heart and by determining by measurement the distance above the heart at which the veins on the back of the hand are seen to collapse.

Eyster and Hooker have devised an instrument which can be used to measure the venous pressure in the superficial veins. The principle of the instrument rests on the use of the visible collapse of a vein on the back of the hand and the measurement of the forces necessary to collapse the vein in centimeters of water.

The instrument consists of a manometer which contains colored water and which is supported on a stand. The instrument is connected to a tube at the end of which is a small glass bell which is fixed over a vein by means of celloidin. A pressure bulb is attached at a Y on the tube. The patient's hand is placed on a level with the heart; the glass is fitted over a prominent vein by means of the celloidin, and pressure is exerted with the bulb. The point of the visible collapse of the vein seen through the glass is read in centimeters on the water manometer. Other more or less elaborate methods have been devised for recording the venous pressure, a full discussion of which will be found in Norris's "Blood Pressure and Its Clinical Applications."* The venous pressure normally varies from 3 to 10 cm. of water. The greatest increase is seen in venous stasis, resulting from cardiac decompensation. Eyster maintains that increased venous pressure is the earliest sign of cardiac decompensation, and that it is the last condition to become normal when compensation is established.

Functional Tests in Relation to Blood Pressure.—When the heart responds to increased bodily activity, not only the pulse rate but the blood pressure rises. The rise is almost entirely limited to the systolic pressure, although the diastolic rises slightly, the pulse pressure is increased, and blood flow is faster. After exercise the pressure returns to normal; this should occur normally in a brief period of time.

Upon this series of facts, tests have been devised by a number of workers. Theoretically, some are correct, but practically all fall short of accuracy. The

* Norris, G. W.: Blood pressure; its clinical applications, ed. 3, Philadelphia and New York, Lea & Febiger, 1917.

work required in executing some of the tests is so violent that there is clinical evidence of functional incapacity. Instruments are superfluous.

Were the arteries a system of rubber tubes with a known coefficient of elasticity, it would be possible to measure accurately the functional capacity of the central pump. But when the vessels are under the control of the vasomotor system, are subject to various psychic influences, and vary in their size and elasticity, no method which has ever been devised is able to do more than approximate the functional capacity of the circulation.

Graüpnér's test, in its original form, has been discarded. The principle was based upon the response to measured work with the legs recorded on a bicycle ergometer. By means of a brake the amount of work done can be measured. Cabot and others have modified this to either climbing a number of steps at a certain rate or walking up an inclined plane at a certain rate. The blood pressure and pulse rate are taken before exercise, immediately after exercise and every half minute, until the above rates return to pre-exercise figures. This has some value, but it is hardly as great as its enthusiastic advocates claim. In this test the blood pressure rises in a normal heart, and the pulse rate increases, but within three minutes it is back to the original figures. A poor response consists in a slow rise with rapid pulse and in a prolonged slow fall. A decline of pressure signifies a failing heart.

Another method described by Katzenstein was based upon the reaction of the heart to the compression of both iliac arteries. This, too, has been discarded. More recently Barringer has used a measured amount of work performed with dumb-bells, or with a steel bar. The dumb-bells weigh from 3 to 20 pounds each. Calculation is based on foot-pounds per minute. For example, two hundred foot-pounds consist in lifting a five-pound dumb-bell above the head twenty times a minute. After exercise the pulse rate and blood pressure are taken every thirty seconds. The exercise is gradually increased up to the limit of mild fatigue by increasing the weight of the dumb-bells. Under normal conditions he notes a delayed rise in systolic pressure after heavy work.

Barringer considers that the delayed rise in systolic pressure is the essential feature. The time when it occurs and the amount of work performed measure the cardiac efficiency. He says, "Our *clinical experiments* demonstrate conclusively, we believe, that in the pulse rate and blood pressure reactions to graduated work we possess a valid test of the heart's functional capacity. If the systolic blood pressure reaches its greatest height, not immediately after work, but from 30 to 120 seconds later, or if the pressure immediately after work is lower than the original level, that work, whatever its amount, has overtaxed the heart's functional capacity, and may be taken as an accurate measure of the heart's efficiency." A study of Barringer's records leaves one unconvinced of the value of his modification of the work test. The author and others have failed to find much help in this method. Practically, the test, used by the Army Cardiovascular Boards in the recent mobilization, gives about as fair a degree of information of functional capacity as the more elaborate tests. This test consisted in hopping on one foot 100 times. The blood pressure and pulse rate were taken in the recumbent posture. Immediately after exercise and every half minute thereafter, the pulse rate and blood pressure were taken. Within two minutes the pulse rate should normally return to within four beats of its former rate, and the systolic pressure should also be back to its original height.

A much more accurate method of measuring functional capacity was employed in the examination of aviators for altitude flying. By means of a chamber in which the oxygen tension could be rapidly reduced to simulate altitudes of thousands of feet, it was found that functional capacity could be very accurately measured. "In the case of well-compensated valvular disease, murmurs develop under low oxygen or become much stronger, and accentuation of heart sounds takes place, indicating hypertrophy of the left ventricle or back pressure through the lungs; the blood pressure is high and the heart is evidently overworking seriously. Often in young men such a heart will be fully as successful as a normal one in meeting the demands made on it in ordinary

life; in fact, overcompensation is the rule rather than a failure to compensate. But under the low oxygen test the underlying defect is revealed.

"In the case of valvular lesions that are less well compensated, the heart is more readily reduced to incompetence; after the period of overwork there is marked cyanosis, excessive discomfort, and insufficiency of the peripheral circulation, most delicately shown by inability to perform well on the psychologic apparatus that forms part of the rebreathing test.

"In subjects with arterial disease, there is a more or less marked rise in blood pressure, owing to inability of the peripheral vessels to make way for the increase of blood flow without throwing a much increased strain on the heart. At the same time there is doubtless insufficiency of the coronary circulation as well, so that between high blood pressure and poor nutrition, the heart muscle soon becomes incompetent; the heart sounds deteriorate rapidly in quality, and the peripheral circulation becomes insufficient" (J. L. Whitney).

The energy index is a term applied by Barach to denote the total force per minute of the heart's action. He takes as the three well-established facts: systolic pressure, diastolic pressure, and pulse rate. He multiplies the addition of the systolic and diastolic pressure by the pulse rate per minute. This he terms the S. D. R. index, and contends that, although it does not measure the work of the heart, it indicates the degree of activity of the circulatory system. Normally, the index is found to be about 20,000 mm. Hg pressure per minute. "A high index means increased cardiovascular effort; either the action of the heart and blood vessels is accelerated because of inability to accomplish their work at a normal rate of activity, or they are fully capable of doing their work, but the resistance to their functioning is great. Either condition is pathologic, and the variation of the index from the normal calls attention to this" (J. H. Barach).

As a matter of fact, there is no method which is applicable to all cases. The problem is still open for solution.

Hypotension.—Constant low blood pressure is a characteristic of certain individuals and seems in no way to limit their activities. Provided the pulse pressure is over 30 mm. Hg, there is no essential reason why persons with systolic pressure of 100 mm. should have any symptoms. However, in many persons there is a train of indefinite symptoms such as headache, feeling of lassitude on slight exertion, mental depression, constipation, etc. Such people are usually of slight build, and have small bones and a long thorax with very acute costal angle. There is a tendency to splanchnoptosis, and general relaxation of musculature. The arteries seem small and are frequently palpable. The hands and feet are cold. The heart is long and narrow and the fluoroscopic shadow of the aorta is quite narrow.

Some of these people have what Sewall calls occult tuberculosis. There is no activity, but there are evidences of a slow fibrotic process which are shown most clearly by means of stereoscopic x-ray plates of the chest. The hilus shadows are large for the age of the person. The linear markings extend radially outward and upward almost to the chest wall and into the apices. Scattered shadows, which are probably calcified, or fibrotic lymph nodes, are discovered in the lungs.

Sewall has also called attention to the change in pulse pressure which is produced by the assumption of either the recumbent or the standing position. The vasomotor tone is so low, especially in the splanchnic vessels, that the pulse pressure falls when the standing position is taken. Either the systolic pressure falls or the diastolic pressure rises; however, the former usually occurs. The result is the same. The volume output of blood is lessened and the coronary arteries are not filled during diastole. Dizziness due to cerebral anemia is common and fainting is not infrequent.

The examination of the thousands of recruits for the army revealed a group of men who had breathlessness, palpitation of the heart, and precordial pain on slight exertion. Mental apathy, cold clammy cyanosed hands and feet, and frequently headaches, were also observed. Blood pressure estimations on these

men showed, as a rule, no hypotension; yet it might have been expected among such constitutional defectives. The subjects of true hypotension have little resistance to disease. They seem particularly prone to infection with tuberculosis; probably many are suffering from "occult tuberculosis."

The causes of essential hypotension are not known. Some have thought that it was due to choline circulating in the blood, but this is disputed and has not been proved. Certain of the cases result from poor ancestry; in some there is syphilis in the antecedents. Graves contends that the scaphoid scapula is a frequent finding in hypotension. The assumption of a functional or constitutional defect in vasomotor control is begging the question, but it is the most which can be said relative to the cause of the condition.

Hypertension.—When the systolic pressure is constantly above the upper limits of the normal for the age and sex of the individual, it is designated as hypertension. Systolic pressure temporarily may be quite high, but it cannot be said to be hypertension unless it maintains a continued elevation. Prolonged hypertension is not a normal state. Sooner or later there are changes in the whole circulatory system.

Systolic blood pressure may vary frequently and as much as 30 mm. Hg. Variations in the diastolic pressure are not so great. In fact, this pressure is quite constant. A rise which is continuous has as much, if not more, significance than a rise in systolic pressure. When the diastolic pressure is found to have a constant reading of 100 mm. or more, hypertension is present, whether the systolic pressure is 170 or 140 mm. In fact, if the diastolic pressure is 100 mm. and the systolic pressure 170 mm., the person may feel perfectly well. However, should the systolic pressure drop to 140 mm., while the diastolic remains 100 mm., there is insufficient pulse pressure, and dizziness or fainting results. The drop in systolic pressure is usually the precursor of a failing heart.

Hypertension and chronic nephritis are not always necessarily associated. It is true that there are always microscopic evidences of kidney disease in every hypertension death. Functionally, many kidneys are normal according to all the usual tests. The criterion is not what the morphologist finds but what the kidneys are capable of doing during life. Kidneys which are functionally normal are for all purposes normal kidneys.

Occasional traces of albumin and hyaline casts in a urine of normal specific gravity do not always signify chronic nephritis. Such occasional findings in persons over fifty are not alone sufficient to diagnose nephritis in the face of normal function.

ETIOLOGY.—Various theories have been advanced to explain the condition, but none has been satisfactory. Many of the cases are accompanied by high diastolic pressure; others are found in which the diastolic pressure is below 100 mm. Hg.

The consensus of opinion at the present time is that the initial lesion is a vasospasm of the arterioles throughout the body. This spasm has a large psychic element to it. There are cases of hypertension which last for years and at autopsy no demonstrable lesions can be found by the microscope. These are unusual cases. In the great majority of cases certain changes take place in the arteriolar muscular coat, leading at first to hypertrophy and later to hyaline deposits such as Gull and Sutton described years ago. Such changes, as Keith and his associates and Murphy have shown, can also be found in arterioles of the pectoral and other muscles. As long as no anatomical changes take place in the artery the condition, as Stieglitz says, is reversible. Pathological changes render the condition irreversible but even then there is usually some element of spasm.

Stieglitz has proposed a very simple test to determine the degree of spasm. With the blood pressure cuff on the arm the patient inhales a pearl of amyl nitrite. The pressure must be rapidly measured as the action of the drug is fleeting. However, with a little practice one can catch the blood pressure at the acme of vasodilatation. The degree of blood pressure drop indicates the part

played by vascular spasm. The drop can be expressed in percentage of the normal. One sees pressures of 220/120 drop to 130/80 momentarily. Other cases show little or no drop, showing that the pathological arteriolar changes have gone to the point where the arterioles are fibrous cords incapable of dilatation. This test is a distinct contribution to the subject and should be used in all but the most seriously ill patients.

What substance or substances produce the vascular spasm, the first stage of arteriolar sclerosis? There is much speculation about this. A great deal of experimental work has been done but thus far we can only say we do not know. We know that certain drugs raise the blood pressure temporarily. Injections of adrenaline and pituitrin (especially extract from the infundibular portion of the gland) also raise the blood pressure. Voegtlin and Macht have isolated a crystalline substance from the blood of man and other mammals which they regard as a lipid, closely related to cholesterol. This substance was recovered from the cortex of the adrenal gland. It increases blood pressure. Whatever the substance is, it seems to be in the circulation and to exert its effect in one of two ways: (1) by stimulation of vasomotor center, or (2) by the direct action either upon the capillary area or upon the muscle cells in the walls of the arterioles. In either case, peripheral resistance is increased. This raises the diastolic pressure and, consequently, the heart must pump harder to keep the blood in circulation.

During the past few years Major and his associates have found that methyl guanidine, a normal constituent of the urine, "is capable of producing a marked and prolonged elevation of blood pressure in animals and in man. A further study of the urine in certain cases of arterial hypertension showed a diminished output of guanidine compounds when compared with normal controls." At present there is no simple or accurate method of measuring the amount of guanidine in the blood. No doubt some method will be devised. If it is suitable only for investigative work, we shall probably be one step nearer in our understanding of one of the causes of chronic increase in blood pressure.

It has been known for generations that interference with the blood supply to the brain causes unconsciousness and use was made of this fact to induce anesthesia for operations. Cushing showed years ago that intracranial pressure caused an elevation of blood pressure and this has been accepted by physiologists, although all cases of increased intracranial pressure in men are not accompanied by elevation of blood pressure.

In 1925 Anrep and Starling by a most ingenious method showed experimentally that deprivation of blood to the brain invariably caused a rise of blood pressure. Starling later suggested the possible pathological significance of the experimental results.

Bordley and Baker in 1926 examined the medulla at the site of the vasomotor center in twenty-four cases. In every case of increased blood pressure they found definite changes in the arterioles. "The intima in most of them (arterioles) was fairly normal, although in some of them it was somewhat thickened. The media showed a variety of changes and in all the arterioles it was obviously thicker than normal; the muscle nuclei stained poorly. Fibrous tissue infiltrated through the media. In some arterioles the media had a homogeneous, hyaline appearance; in others a granular deposit separated the muscle fibers of one side, forcing the lumen into an eccentric position, almost obliterating it." Gull and Sutton in their classic paper had already described exactly the same lesions in the little vessels of the pia mater where they said the lesions of arterio-capillary fibrosis could be readily found.

The localized character of the arteriolar changes was striking. In the same microscopic field in a section of the medulla, there would be a practically normal and a thickened arteriole. In widespread arteriosclerosis changes indistinguishable in character were found in the kidneys of both cases of hypertension and normal pressure. But in cases of the latter type the medullary vessels were not found to be at all affected. The authors suggest that "it is altogether likely that when these vascular changes take place in the brain stem, there is an explanation for the occurrence of hypertension."

If this careful piece of investigation is confirmed, it will put hypertension on an anatomical basis, and at least take the explanation for its continued presence out of the realm of speculation. The cause of the arteriolar changes remains still obscure. In spite of all the literature on the subject, no more is known now than when Johnson and Gull differed as to whether the hypertension or the arteriolar changes came first.

Destruction of the suprarenal gland as occurs often in tuberculosis leads to the well known syndrome of Addison's disease. Hypotension is characteristic of this condition. Occasionally hypertension is associated with tumors of the suprarenal gland. This is not common and raises the question of the influence of the suprarenal medullary secretion in keeping up prolonged hypertension.

Chronic Focal Infection.—While chronic focal infection has been held responsible for all the ills to which flesh is heir and many an innocent pair of tonsils and many a perfect tooth have been sacrificed to this Moloch, yet it can not be denied that there are hidden foci of infection which do occasionally have definite etiologic relationship to groups of signs. Among these signs is hypertension. Fontaine reported that in 100 cases, most of whom were in women, six showed hypertension and that the removal of teeth with apical abscesses reduced the blood pressure in these cases. One must always bear in mind that as blood pressure is subject to wide fluctuations which have no particular significance, and that as irritations and psychic factors can elevate pressure, one must be cautious in attributing a reduction of high blood pressure to any one measure. The writer can not say that he has seen more than one chronic infection definitely connected with increased blood pressure. This is chronic gallbladder disease. At first this was thought to be coincidence, but as the evidence accumulated it seemed reasonable to conclude that one form of hypertension had a cause toxic in nature which probably caused a spasm of the arterioles of the body or of the abdominal viscera only and forced the heart to do more work. In the favorable cases the removal of the gallbladder is followed by decrease of the blood pressure usually to within average normal limits. The systolic is elevated to a much greater degree than the diastolic.

As so many women of the menopausal age have gallbladder disease, it is frequently impossible to decide in any given case whether the hypertension is the result of endocrine disorders or the result of chronic toxemia. Such cases require most intensive study.

Overweight and Obesity.—While overweight in itself is not in any sense a cause of hypertension, it is interesting that the overweight persons in any large series show a higher ratio of hypertension cases. Conversely, in the routine examination of several thousand cases, the one outstanding characteristic of the hypertensive cases was overweight (Fiske). The obese do not necessarily have hypertension but in really obese individuals about half are found to have increased pressure for the age group in which they belong. Some of the obese are definitely hypothyroid cases. This should always be borne in mind and careful basal metabolism estimations made. Under no circumstances should thyroid extract be given to reduce flesh unless the increased fleshiness is proved to be the result of thyroid deficiency.

Vaquez calls attention to the frequent association between hypertension and uterine fibromata. He quotes statistics of 416 women observed over a period of five years during the development of the fibromata. Increase in pressure was found 240 times.

Chronic Constipation.—There has been a general impression that constipation with the possible absorption of some poisonous substances is often the cause of increased blood pressure. Alvarez and his collaborators have carefully studied this supposed relationship and find that it is nonexistent. Constipation in men has absolutely no effect on the blood pressure. In women the authors find a slightly lower mean blood pressure.

Influence of Sex Organs.—The menopausal hypertension has already been noted. Certain disturbances in the sex organs of younger women apparently affect the blood pressure. According to studies by Alvarez and Zimmerman,

women with poor ovaries are likely to develop hypertension in early life. The exceedingly high pressures are due to nephritis. Some of the authors' conclusions are: "Well proportioned women have systolic pressures that average 10 mm. higher than those of the thin, and pressures in the stout average 12 mm. higher than in the well proportioned. . . . The sexually abnormal have pressures that average considerably higher than do those of the sexually normal. As the sexually abnormal tend to get married a little late as compared with their normal sisters, we find that single women have pressures averaging a little higher than those of the married women. A masculine distribution of body hair, sexual anesthesia, fibroids of the uterus, thyroid disease and pelvic conditions requiring ovariectomy or hysterectomy are associated with high average pressures. The average pressure for all ages in women who seem to be sexually normal is 134.5 ± 0.7 mm. of mercury. The average in the twenties is 122.1 ± 0.7 ; in the thirties it is 125.8 ± 0.7 ; in the forties it is 135.3 ± 1.2 , and after 50 it is 154.4 ± 1.7 mm.

Hypertension is regarded by the author as a physiological response of the heart, directed toward maintaining the circulation in equilibrium under conditions which tend to produce vasoconstriction in large areas and to deprive these areas of blood. Hypertension is, then, a conservative process, but like many processes in the body, the conservative feature may in time become of real danger to the individual. Unless hypertension developed, in many cases the individuals would not live. There must be enough force to drive the blood through the body.

HYPERTENSION IN YOUNG PEOPLE.—Although hypertension is usually found in people after the age of forty, it is by no means confined to that group. Many cases are seen below the age of twenty and it is not so uncommon to see children 9 or 10 years old with high blood pressure. In general it can be said that cases of juvenile hypertension belong in the chronic glomerular nephritic group. A history of scarlet fever often is obtained or some other febrile disease or a spontaneous acute nephritis may initiate the kidney changes which lead to hypertension.

The pathological process in the kidneys of these cases runs a rapid course with necrotizing changes in the walls of the arterioles. This type might well be called "malignant hypertension."

Occasionally no symptoms are present and the condition is accidentally discovered. Persistent headache or undue shortness of breath on exertion is often the only symptom. The pressure picture is high. The kidneys are functionally deficient by all tests. The eyegrounds often show the changes characteristic of nephritis.

The prognosis is grave. How long young people live with hypertension can not be accurately stated, but when symptoms appear and eyeground changes are present, death may be expected within a year or eighteen months.

Treatment is without avail. Measures should be directed towards the comfort of the patient. Diet should not be too restricted.

CLINICAL VARIETIES.—*Changes in the Heart Due to Hypertension.*—The circulation in its simplest analogy is like a pump and a number of distributing tubes which branch extensively. The velocity at the aorta is rapid; in the capillaries it is slow. A certain amount of blood, about 75 to 90 cc. (Howell), is expelled at every normal systole. When the pump has to do more work, it acts as any other muscle does which is called upon for extra continuous work—it hypertrophies, provided that there has been at some time dilatation of the left ventricle. The fibers of the heart become longer and larger, and consequently, the left ventricle becomes thicker and heavier. At the same time the cavity of the ventricle is increased in size. More blood is thrown out at every systole. The peripheral resistance forces up the diastolic pressure. The systolic pressure increases to such an extent that the pulse pressure rises beyond the normal figure. At the same time that the heart is gradually becoming enlarged, the nutrition of the muscle suffers and connective tissue is gradually formed, thus actually paving the way for future weakness. The aortic valves become thicker, due to the extra strain put upon them.

While what has been just written is true in some cases, it will not hold for all. Cardiac hypertrophy appears to be the result of a preliminary stretching of the muscle fibres plus an increased load. It is surprising how little hypertrophy can be found by the most careful x-ray examination in a patient who has had hypertension for several years. It is not known just when or just how the heart increases in size in these cases. Possibly increased sudden strain in the course of a hypertension starts dilatation. However, one must not expect always to find heart hypertrophy with hypertension.

Changes in the Arteries Due to Hypertension.—Whether one believes that the heart first hypertrophies and produces changes in the arteries or that the arterial changes precede the cardiac, the changes in the arteries in hypertension are great. The distributing channels show a diffuse fibrous arteriosclerosis.

The vessels are often somewhat tortuous. In some cases they are firmer and smaller than normal; in other cases they are thicker and larger than normal. The fibrosis generally affects the media and replaces the elastic fibers so that the blood no longer flows through an elastic tube but through a more or less rigid one. Hence greater head of pressure must be maintained at the heart to force blood through these less elastic channels.

In the small arterioles, both intima and media are affected. The channels are narrowed by intimal proliferation, and the contractility and distensibility of the vessels are lessened by the loss of muscle tissue. Therefore, a considerable force is necessary to drive the blood through the narrowed channels in order that it may reach the cells of the organs. Probably the enormous capillary bed is narrowed in large areas and offers further resistance to the onflow of the blood.

Hypertension may be of serious moment to diabetics, inasmuch as it may raise the renal threshold for sugar excretion.

Hyperpiesis.—This is a term, meaning "excessive pressure," which Sir Clifford Allbutt proposed as a designation for those cases of hypertension which are not due to evident renal or cardiac disease. There is an arteriosclerosis, which is the consequence of tensile strength, of excessive arterial blood pressure persisting for some years.

HIGH PULSE PRESSURE.—In every case of fully compensated hypertension there is increased pulse pressure. Normally, the arch of the aorta, already filled with blood, and still contracting on the column of blood to force it onward, is suddenly and violently distended by the blood from the left ventricle. It is somewhat stretched, and as soon as diastole begins, it contracts upon the column of blood, held at one end by the closed aortic valves. Pulse pressure measures the actual driving force which propels the blood to the periphery. If, then, the peripheral resistance is great, there must be a greater driving force at the pump. In all high pulse pressure cases four conditions are found:

- (1) Increase in the size of the cavity of the left ventricle. There is more than 90 cc. of blood ejected at every systole.
- (2) Increase in the width of the aortic shadow seen with the x-ray.
- (3) Increase in the size of all distributing arteries, carotids, brachials, radials, femorals, renals, celiac axis, etc.
- (4) The impairment of the percussion note over the manubrium sterni and bronchial to tubular breath sounds heard with the stethoscope.

VARIETIES OF HYPERTENSION.—All cases of hypertension are not due to the same cause or causes. There are several varieties. They may be roughly divided into the subacute and chronic hypertension cases.

Subacute Hypertension.—Under this heading come the hypertension of pregnancy and of eclampsia. In eclampsia the pressure picture is high, but after the uterus is emptied, the blood pressure in many cases returns after a few weeks to its original level. Focal infections, exophthalmic goiter, and neurotic states may show hypertension until the cause is removed. Occasionally brain tumor, if complicated with asphyxia, and intracranial pressure from fracture of the skull, produce hypertension.

The hypertension found in many women at the menopause is at times not a chronic process. While these conditions are important, they are not as serious as are the chronic hypertension cases, which are divided into at least three groups.

Group 1.—Chronic Nephritis.—These are the cases with high pressure pictures, i.e., high systolic (200+) and high diastolic (120–140+). The pulse pressure is much increased. The palpable arteries are hard and fibrous. There is puffiness of the lower eyelids; this condition is most pronounced in the morning on rising. Polyuria with low specific gravity, and nycturia are present. There are almost constant traces of albumin in the urine, with hyaline and finely granular casts. Functionally, these kidneys are much under normal. The functional capacity determined by the dilution and concentration test method shows a marked deviation from the normal fluctuations of specific gravity. The phthalein output is below normal. As the case advances, the phthalein output becomes less and less, until a period is reached when there are only traces, or when there is complete suppression at the end of a two-hour period. There is fixation of specific gravity at a low point 1004 to 1006 with marked polyuria. Such patients may live for ten weeks (as, for instance, in one of the author's cases), continually showing mild uremic symptoms, and then they may suddenly pass into coma and die.

The terminal condition in cases in this group is either uremia or cardiac decompensation (so-called cardiorenal disease). Cerebral accidents may happen to a small number. It is the author's opinion that the term *cardiorenal disease* should be applied only to this group. However, the author once believed that all high systolic pressure cases should be diagnosed as chronic glomerulonephritis of some definite degree. From the purely pathological standpoint such a diagnosis may be correct, but from the real, the functional standpoint it is far from being the true condition of such cases. In this group, there is marked hypertrophy and moderate dilatation of the left ventricle, with dilatation and nodular sclerosis of the aorta. The kidneys are firm, red, small, coarsely granular, the cortex much reduced, and the capsule adherent. Cysts are common. It is the familiar secondary contracted kidney. Mallory calls this capsular glomerulonephritis. The etiology is obscure. Often no cause can be found. Again, there is a history of some kidney involvement following one of the acute infectious diseases, or the nephritis of pregnancy.

Group 2.—Essential Hypertension; Vascular Hypertension; Hyperpiesia.—One might designate this group as essential hypertension, or as the hereditary type, although there is not always such a history in an antecedent. This group includes the robust, florid, exuberantly healthy people. They often boast that they have never had a doctor in their lives. They are usually thickset or very large and fleshy. The pressure picture is exceedingly high. The pulse pressure is moderately increased. The arteries are rather large, fibrous, and often quite tortuous, although this is not always the case. Some of these individuals have small, hard, fibrous arteries. As a rule, there is no puffiness beneath the eyes, no polyuria, and no nycturia. The urine is of normal amount, color, and specific gravity. Albumin is rarely found and then only in traces; but careful search of a centrifuged specimen invariably reveals a few hyaline casts. The phthalein excretion is normal or only slightly reduced. The kidneys excrete salt and nitrogen normally. The dilution and concentration test shows no fixation of specific gravity. It is in this group that apoplexy is found most frequently. The rupture of the vessel occurs when the victim is in perfect health, often without any warning. Occasionally, when such a patient recovers sufficiently to be out of bed, cardiac decompensation develops later and he dies as a result of the cardiac complications. Pathologically, the hearts of such persons reveal the most enormous hypertrophy of the wall of the left ventricle. The cavity is somewhat enlarged, as is always the case when the pulse pressure is increased, but the size of the cavity is not the striking feature. The aorta is fibrous, thick-walled, and the arch is slightly dilated. There are patches of arteriosclerosis. One patient, seen only at autopsy, had a rupture of

the aorta just above the sinus of Valsalva; death had been due to hemopericardium. In such cases the kidneys are of normal size, dark red, and firm; the capsule strips readily, the surface is smooth or finely granular, and the cortex is not decreased. The pyramids are congested, and red streaks extend into the cortex. Microscopically, the capsules of the glomeruli are a trifle thickened; a few show hyaline changes. There is rather diffuse, mild, round cell infiltration between the tubules. The tubular epithelium shows little or no demonstrable change. The arterioles are generally the seat of a moderate thickening of the intima and media, but it is not usual to find obliterating endarteritis. There is evidently a diffuse fibrous change which has not affected either the tubules or the glomeruli to any great extent.

The kidneys in many cases of this group gradually contract. They are hard, red, with fine granulation on the surface. In cut section the cortex is thin and few glomeruli are seen. Microscopically, the glomeruli are completely hyalinized with dilatation of the corresponding tubules and loss of epithelium. The afferent arterioles show most extensive changes, hyalinization, intimal proliferation often leading to complete obliteration, the so-called endarteritis obliterans. Volhard calls this red hypertension.

When these patients with acute cardiac decompensation are seen, there is of course, much albumin in the urine, and many casts, and the phthalein output is, for the time being, decreased.

Group 3.—Arteriosclerotic High Tension.—This might be called the arteriosclerotic high-tension group. Such patients are usually over fifty years of age. They are men and women who have led strenuous and dissipated lives, both physically and mentally. Often they have had periods of great mental strain. Many men in this group have been athletes during their young manhood. Many have been fairly heavy, although not excessive, drinkers. They are usually well-nourished and inclined to stoutness. The pressure picture presents high systolic pressure with normal or only slightly increased diastolic pressure, usually below 100 mm. Hg, and high pulse pressure. The arteries are large, full, fibrous, and usually tortuous. The heart may be large, the apex being far down and pointed outward. There is no polyuria; nycturia is uncommon, being, in fact, quite the exception. The urine is normal in color, amount, and specific gravity. Albumin is found only in rare instances, and hyaline casts are not invariably present. The phthalein excretion is quite normal, as is the excretion of salt and nitrogen. The terminal condition in most of the patients in this group is cardiac decompensation. They may have several attacks from which they recover, but each succeeding attack is produced by less exertion than the preceding one, and their control becomes more and more difficult. Eventually the patients become bed- or chair-ridden, and finally they die of congestive heart failure. Occasionally patients in this group may have a cerebral attack, but in the author's experience this is uncommon. Pathologically, the heart is large, at times a true *cor bovinum*, and is dilated and hypertrophied. The cavity of the left ventricle is much dilated. The aorta is dilated and sclerosed.

The kidneys are increased in size, are firm, dark red in color, and have fatty streaks in the cortex. The capsule strips readily and the cortex is normal in thickness, or only slightly increased. The organ offers some resistance to the knife. The microscope shows small areas scattered throughout where the glomeruli are hyalinized, the stroma full of small round cells, the tubules dilated, and the cells almost bare of protoplasm. Naturally the tubules are full of granular cast material. Also, the arterioles show extensive intimal thickening, fibrous in character, with occasional obliterating endarteritis. One has the impression that the small sclerotic lesions are the result of anemia and gradual replacement of scattered glomeruli by fibrous tissue. For the most part, the kidney, except for the chronic passive congestion, appears to be quite normal. One can readily understand that in such a kidney, function could not have been interfered with. Some authors do not separate the last two groups but call them together "vascular hypertension."

Hypertension Climacteric.—Many authors have called attention to the increase in blood pressure in women at the menopause. Riesman gives the following points common to the group:

- (1) The patients are usually stout, overweight and undersized.
- (2) They have borne many children.
- (3) They have neither a history nor any stigmata of syphilis.
- (4) They are over forty-five years of age, the greater number being between fifty and sixty years.
- (5) They are practically all constipated, and some of them suffer from intestinal indigestion.
- (6) Up to a certain point, they show an amazing tolerance to pressures of high degree.
- (7) In most cases the heart is enlarged, chiefly to the left.
- (8) The arteries are soft, and even the retinal vessels rarely show any involvement.
- (9) The kidneys, as far as it is possible to determine, are competent.

These cases belong to the group of vascular or essential hypertension. The element of vascular spasm is marked. Amyl nitrite usually reduces the blood pressure to or near normal. Probably these cases have some relation to the endocrine gland changes in women of this age group but there is no actual proof of this.

The symptoms which accompany such increased tension are thought by some to be due to the lack of inhibitory action of the ovarian secretion upon the thyroid, pituitary, and adrenal glands.

Cardiorenal Disease.—The author believes that this term should be reserved exclusively for those cases of chronic glomerulonephritis which develop decompensation as the result of the failure of the heart to maintain the hypertension necessary to life. In such cases the cardiac symptoms dominate the clinical picture. Under such circumstances the blood pressure becomes of value in diagnosis. The estimation of blood pressure in decompensation is difficult and only fairly accurate. However, the few very high systolic pressure tones which are heard over the brachial artery, below the blood pressure cuff, reveal that the case is not one of pure cardiac origin. As the patient recovers compensation, the hypertension becomes definite.

Gull and Sutton, many years ago, gave the name arteriocalillary fibrosis to the cases of chronic nephritis. They conceived the idea that the pathological lesion was a general one, affecting not alone the kidneys, but the entire vascular system, the kidneys being affected simply in the course of the process.

The essential facts remain that in chronic nephritis there are widespread changes in all the arteries and in the heart, so that the heart is finally worn out by the attempt to force blood through the constricted vascular channels. Often the diastolic pressure is 180 or even 200 mm. In other words, in order to open the aortic valves the heart must perform an amount of work equal to or even greater than the normal heart performs at its maximum contraction. It is surprising for how long a time—years even—the heart is able to endure such a strain as is thereby placed upon it.

Meltzer called attention to what he termed "factors of safety" in the human organism. Here there is striking evidence of the factor of safety in the heart. In such a heart the reserve power is necessarily small. The organ is always approaching its maximum capacity and cannot suddenly take on a load without becoming dilated. This accounts for the sudden cardiac collapse in a nephritic patient who has had no intimation that he was ill other than necessity of rising once or twice during the night to urinate. A bronchitis or a sudden physical strain destroys the delicate balance of the circulation and decompensation results.

Malignant Hypertension.—There are cases of rapidly advancing hypertension found at all ages, but chiefly in the fourth and fifth decades, some of which appear to be superimposed upon benign vascular hypertension, others apparently develop *de novo*. As a "benign" hypertension may eventually be accompanied by kidney changes and become "malignant," the use of the latter term

should be used for the cases of rapidly advancing kidney changes in any hypertension. Keith has attempted to separate a distinct group which he calls "malignant" hypertension but his contention is not convincing. Volhard and Fahr first drew particular attention to such cases. Occasionally a case is seen in a young person in the twenties.

Etiology is unknown and no method of treatment avails against the downward course of the disease. Microscopical examination of the organs reveals changes in the arterioles described in 1872 by Gull and Sutton.

As long as the eyegrounds of the hypertensive case show no blurring of the margins of the discs, no exudate along the vessels or no hemorrhages, as long as the functional capacity of the kidney as measured by the various tests (phenol-sulphonephthalein, dilution and concentration, urea clearance test, nonprotein N in blood) is normal, and as long as there is the reaction to amyl nitrite down to or reasonably near normal, the case is vascular hypertension and the prognosis is usually good. However, in some cases of what have been for years simple vascular hypertension and in young people especially under twenty years old, a state of affairs is found which totally alters the prognosis. The pressure is high, both systolic and diastolic, it can be reduced little or not at all with amyl nitrite; the kidney shows definite functional deficiency and the eyegrounds undergo marked changes. These last consist in edema of the discs and of the retinæ, narrow, irregular and disappearing arterioles, dilated veins constricted where the arteries appear to cross them, cottony exudate along the arterioles, and hemorrhages into the retinæ. This is what is called "malignant hypertension." Some think that it is only the end stage of a benign hypertension. This raises the question of how a process can be benign and malignant at the same time. The difference being only one of degree, then all should be benign or malignant. But as it seems nonsensical to attribute to a benign cause such a serious result as death, some (Bell and others, including the author) regard all hypertension as the result of a slow chronic infection acting for the most part on the afferent arterioles of the kidney. The lesions are hypertrophy of the muscle fibers, hyaline deposits in the media, heaping up of intimal cells at times to complete obliteration of the lumina of the arterioles and small patches of necrobiosis of the vessel walls. The corresponding glomeruli are filled with new connective tissue cells, capillaries are destroyed or complete hyalinization results, depending upon the state of the supplying arteriole. All these lesions can be found in the kidneys of those dying from the kidney complications of malignant hypertension or in the kidneys of those known to have had benign hypertension and who have died from some other disease.

SYMPTOMS OF HYPERTENSION.—Hypertension is compatible with active and vigorous bodily and mental health. For an unknown period of years, perhaps, there has been a gradual increase in pressure. The increase is not without fluctuations. Diet, mental worry, and attacks of constipation have their acute effect, but there is a general tendency to a constant increase of pressure.

When symptoms occur, they may be confined to one system, for example, the cardiovascular, or renal, or nervous system, etc., or they may show complications in two or more systems.

The following groups may be recognized: (1) cardiac, (2) renal, (3) gastrointestinal, (4) nervous, and (5) ocular.

Cardiac.—This group is characterized by dyspnea on slight exertion; cough; edema of the ankles, which may be worse at night and entirely absent in the morning; anginal attacks; precordial distress; feeling of effort in taking a long breath; and finally, great dyspnea, cough, bloody expectoration, anasarca, scanty high-colored urine, etc.

Renal.—This group is characterized by nocturnal polyuria of pale urine, cramps in the muscles, puffiness beneath the eyes, headache, and later by twitchings, convulsive seizures, sudden blindness, etc.

Gastro-intestinal.—Flatulence, distress after eating, and a tendency to constipation are marks of this group.

At the present time, when the sphygmomanometer is so widely employed, pa-

tients with hypertension complaining of gastro-intestinal or of respiratory symptoms are not as frequently overlooked as they undoubtedly were in former days.

Nervous.—This group is distinguished by irritability of temper, nervousness, inability to concentrate the mind, flashes of temper, change of disposition, headaches, insomnia, and later by transient attacks of unconsciousness with temporary paralysis, larval apoplexies (Allbutt), and apoplexy.

Ocular.—Failing vision, retinal hemorrhages, and sudden amaurosis differentiate this group. The arterioles in the fundus of the eye are the only small arteries which are easily visible to the trained observer with the ophthalmoscope. Examination of the ocular fundi should be a part of every routine physical examination where present hypertension is found or past hypertension is suspected. As stated previously, the state of the peripheral arteries is no criterion of the existence of hypertension. Far otherwise is it with the arterioles of the fundus oculi. There is, according to all authors, a definite relationship between the retinal vessel sclerosis and hypertension. Further, when these vessels are evidently sclerosed but the systemic blood pressure is not elevated correspondingly, it is evidence that hypertension has been present and that the heart is the seat of serious myocardial changes. This is of value in prognosis.

The combination of hypertrophied heart with the apex downward and to the left, ringing second sound at the aortic cartilage, signs of dilated aorta and high pressure picture are readily found and indicate long-standing hypertension. It should be our aim to anticipate this advanced stage if possible. Early recognition does not rest altogether with the physician. Some men are fortunate enough to present themselves for life insurance examinations. Practically all companies now require a blood pressure estimation, although some require only the systolic pressure. The fact that the applicant desires life insurance is usually evidence that he feels well and considers himself healthy. He works hard and plays hard. Others are not as fortunate in finding out that they have true hypertension while still free from all symptoms. They do not seek the advice of a physician until they notice one or more symptoms. They are often incredulous when told the true nature of their trouble.

There seems to be only one method of discovering the early cases of hypertension. People must be carefully examined at least once a year after they have reached the age of forty. The dentists now send cards to their patients reminding them that six months have elapsed since their teeth were last examined. It should be possible for physicians to urge yearly examinations upon their patients. Only in this way will we be able to curb the advancing hypertension before it reaches the point of permanent injury to the cardiovascular and renal systems. Until the physician is recognized as the guardian of health, as well as the restorer to health, there will be no decrease in the number of advanced cases of hypertension.

Treatment.—Since hypertension is considered to be a compensatory process, there is no more reason to treat it *per se* than to treat a case of compensated valvular lesion. A certain amount of hypertension is absolutely necessary to the individual's well-being. Were it possible to reduce the high pressure to normal, there would not be sufficient driving force to send the blood to the vital organs in the brain, and cerebral anemia would result. The high pressure is, however, a combination of the necessary hypertension and the hypertension due to some added factor. It is this latter element in hypertension which we should endeavor to eliminate. In hypertension which presents no symptoms and which is accidentally discovered, it is necessary only to regulate the **hygiene and diet**. Most of these patients eat too much and take too little relaxation. It is the author's belief that meat of all kinds should be limited but not prohibited. People habitually eat too much. At rest the average man can keep in health on 2,000 calories daily. Certainly 2,500 calories should not be exceeded when the individual is moving about in normal activity. It would be distinctly helpful if patients were fed on a caloric basis rather than by the usual haphazard method. The diet should consist of carbohydrates and fats, and large potations of water at meals should be prohibited. A heavy meal causes a distinct rise in

pressure. **Rest** for half an hour after meals is helpful. Mild open-air **exercise** should be urged.

All evident foci of infection in teeth, tonsils, and accessory nasal sinuses should be thoroughly **eliminated**. Probably chronic infection in the gall-bladder and appendix should also be carefully investigated. Of all the chronic foci of infection, the teeth unquestionably are the most important. Abscessed and devitalized teeth should be removed. **Hydrotherapy** is useful. Hot baths as well as very cold ones are to be avoided. An occasional **sweat bath** under supervision is indicated. **Massage** is also to be recommended. A sojourn at a sanitarium where hydrotherapy and massage are systematically given is often of great benefit. **Electricity** has been used to reduce pressure. The high frequency current is the method most frequently employed. Autocondensation also has its ardent advocates. These methods are helpful, but the evidence that they actually reduce hypertension and keep it within reasonable limits is lacking.

Some drugs appear to be of value in certain cases. The nitrites certainly do not help except temporarily; however, **erythrol tetranitrate** has the longest action in the body. Yet no one would seriously contend that this drug should be given except in selected cases. **Potassium iodide** in 1 gram (15.43 grains) doses twice or three times daily is often given, but the results are variable.

Stieglitz highly extols **bismuth subnitrate** in 5 grain (0.3 gm.) doses three to four times daily. This is given for weeks or months, gradually reducing the dose until none is given. He claims that he has results and that they last some months. He has proved that the subnitrate is decomposed in the intestine to the nitrite and thus the vasodilator action of the nitrite is continuous. The author has not been able to duplicate the good results claimed by Stieglitz. When the hypertension is due to toxic spasm of the arterioles, frequent **purgation** and administration of benzyl benzoate do lower the pressure picture. However, it seems futile to give a drug which only temporarily reduces pressure and does nothing to remove the cause of the hypertension. **Sodium** or **potassium sulphocyanate**, the former in 3 to 4 grain (0.18-0.24 gm.), the latter in 1 to 2 grain (0.06 to 0.12 gm.) doses three times daily, may be used. The potassium salt is said to be somewhat toxic; hence care should be used in dosage. With these two drugs, particularly the potassium salt, good results have been obtained. They should be given by the method of gradual withdrawal and checking the blood pressure.

After all, the most efficacious treatment is a combination of hygiene, diet, and attention to the bowels, in conjunction with the removal of all proved foci of infection. When the various final accidents occur, they are to be treated as indicated in the sections dealing with uremia, decompensation, apoplexy, angina, etc.

PROGNOSIS.—As long as hypertension is devoid of symptoms, and is accidentally discovered in a routine examination, the prognosis is uncertain. In the midst of apparent health there may be apoplexy, decompensation or uremia. An apoplexy is not necessarily fatal. Pasteur lived for twenty-five years after a hemiplegia. A cardiac collapse is a serious matter and renders the prognosis grave. Patients rarely live a year after the first attack of cardiorenal disease. An attack of uremia is also a grave accident. As a rule, the patient dies within a year, although there are notable exceptions.

Occurrence in Various Conditions.—**BLOOD PRESSURE IN ACUTE INFECTIONS.**—In all acute infections the blood pressure either shows no change or is slightly lower than in health. At times, at the onset, the diastolic pressure may be lowered and the pulse pressure slightly increased. As the disease progresses the pressure varies with the length of the illness. In a brief illness there is little change. In typhoid fever, for example, there is a considerable fall in the systolic pressure, and the diastolic also falls somewhat in the beginning of convalescence. The pulse pressure is so low that any attempt to rise from the recumbent position brings on dizziness. In unfavorable cases the systolic pressure falls, the pulse pressure is decreased and, as death approaches, the systolic rapidly falls to meet the diastolic, and circulation ceases.

In pneumonia Gibson first called attention to the ratio of pulse rate and blood pressure. When the arterial pressure expressed in millimeters of mercury does not fall below the pulse rate per minute, the prognosis is still favorable. Should it fall appreciably below the pulse rate, it has an unfavorable prognostic import. The rule is useful in many cases, but cannot apply to all. If the blood pressure when the patient was healthy were known, it would be of far greater value. In all cases the sounds heard in the auscultatory phenomenon are of value. As long as the tones are sharp and clear, the heart is usually holding its own. When the third tone, especially, becomes soft and muffled, the first sound at the apex of the heart is usually impure and muffled, and the conclusion is justified that the heart is weakening.

BLOOD PRESSURE IN CHRONIC INFECTIONS.—In the commonest chronic infection, tuberculosis of the lungs, the blood pressure varies somewhat with the stage of the disease and the type of the individual. It has already been said that in the so-called occult tuberculosis there is hypotension. In the average incipient case in a previously healthy person, the pressure is within the normal limits. As the disease progresses there is definite hypotension and usually a decreased pulse pressure. In gout there is apt to be hypertension, and in most gouty individuals there is also chronic nephritis, either of the interstitial or of the diffuse variety.

In chronic arthritis of the deforming type the pressure is usually low. In most of the chronic infections the tendency is toward low pressure, but there are many exceptions to this rule. Why a chronic focal infection, for example, should in one person apparently cause hypotension and in another cause hypertension is not altogether explainable.

BLOOD PRESSURE IN SURGICAL CONDITIONS.—All anesthetics do not affect the blood pressure in the same manner. An anesthetic is dangerous because of the narrow margin between a well-sustained pressure and a sudden drop in pressure. Among the common methods of anesthesia, the consensus of opinion now establishes the following in the order of their safety: nitrous oxide-oxygen, ether, ethylene, and chloroform. The last is especially dangerous because there is such a narrow margin between safety and sudden danger.

With any general anesthetic the pressure should remain constant during the anesthesia. Signs of danger are the falling of the systolic pressure and the increase in pulse rate. The diastolic pressure may rise slightly, but the decrease in pulse pressure is almost entirely due to the systolic fall. When the pulse pressure reaches 20 mm. Hg, the patient is in danger. The indication given by the blood pressure is more certain and occurs earlier than any other sign. No anesthesia should be given unless the blood pressure cuff is on the arm and frequent readings at short intervals are taken.

Stethoscopes may be obtained with long tubing and a bell which is fixed to the arm over the brachial artery. The anesthetist can not only obtain the systolic and diastolic pressure quickly, but he can tell by the tones of the phases whether or not the heart is weakening. A well-given anesthetic with ether usually raises the blood pressure at first. As the anesthesia deepens, the pressure becomes the same as during waking hours and remains there with slight fluctuations throughout the anesthesia. If the anesthesia is light, pulling on the parietal peritoneum causes a sharp rise. Rough treatment of the structures around the gallbladder may bring on a slight fall. Even in deep anesthesia, pulling on the structures around the celiac axis where the solar plexus lies is evidenced by fluctuations in the blood pressure. In the case of nitrous oxide-oxygen, if well given, there is less change than in that of ether. The initial blood pressure rise is often absent. There is no struggling, but the patient falls into rapid unconsciousness. The chief danger here lies in a fall in the systolic pressure and a rise in the diastolic, due to the asphyxia.

With chloroform there is often a fall during the early stages of anesthesia. During full anesthesia a marked fall often occurs. This renders chloroform very dangerous. The fall usually ceases if the patient is managed properly, but it may suddenly drop further and death may rapidly supervene.

PULMONARY TUBERCULOSIS.—The blood pressure in pulmonary tuberculosis is usually not changed in the early cases, although in some incipient cases or in occult tuberculosis, it often is lower than the average normal range for the age and sex. In advanced and cachectic cases it is naturally lower. High blood pressure and pulmonary tuberculosis appear never to be associated together. This has led to the belief that tuberculin injections would reduce hypertension of the essential (vascular) type. Actual trial of this theoretical therapeutic procedure has not led thus far to any lasting results.

LUMBAR PUNCTURE.—In this operation there is usually a slight rise in pressure, which accompanies the skin puncture, and which increases when the dura is punctured. "Withdrawal of cerebrospinal fluid *per se* tends to lower the blood pressure, but the net result of lumbar puncture is to raise it for at least twenty minutes afterward" (Gray and Parsons). A fall in blood pressure is a signal for the immediate withdrawal of the puncture needle.

SHOCK.—In surgical shock the patient bleeds into his capillaries, which become engorged, and stasis results (Cannon). The blood pressure falls rapidly. If hemorrhage is combined with shock, the fall may be greater, but shock alone, or hemorrhage alone, is capable of producing a fall so great that death results. McKesson's formula is that "a typical case of shock is characterized by a diastolic pressure of 80 mm. or less, a pulse pressure of 20 mm. or less, and a pulse rate of 120 or more per minute."

BLOOD PRESSURE IN OBSTETRICS.—Normal pregnancy has no appreciable effect upon the blood pressure. However, so important is the gradual rise of pressure in denoting toxemia that no one who practices obstetrics should fail to make frequent use of the sphygmomanometer. In order that a woman may be properly carried through a pregnancy, she should be seen within three months of conception. Then the blood pressure should be taken. If the pressure is normal, it will be necessary to take it only once every two weeks or every month for the next four months. If at any time the pressure shows a rise, it should be taken daily until it falls—an indication that there was nothing wrong—or until it gradually rises, when the physician should begin to treat the patient for toxemia.

First, Lynch, and many others have demonstrated the great importance of blood pressure in pregnancy. While eclampsia is possible when the blood pressure is normal, this is the exception. A rising blood pressure is more indicative of the onset of eclampsia than all the urinary examinations. Both systolic and diastolic pressure rise. This is the most typical example of a toxemia producing widespread arterial constriction (or capillary constriction). It is an acute process which, if properly treated, disperses and leaves the woman in most cases apparently without complications. However, if kidney damage is present, there is no return to normal. During normal labor the systolic pressure rises on account of muscular exertion. After labor there is apt to be a general fall of the pressure picture, due to exhaustion and to loss of blood. The pressure quickly returns to its normal figure if the puerperium is uncomplicated.

BLOOD PRESSURE IN BLOOD DISEASES.—There are no particular changes in blood pressure in diseases of the blood, except in anemias when the pressure is apt to be low. There are many exceptions to this statement. A falling blood pressure is a bad omen and a falling pulse pressure is a sign of heart failure.

BLOOD PRESSURE IN CARDIAC DISEASES.—Blood pressure in cardiac diseases has been discussed under the various sections dealing with these diseases. Only one or two points will be emphasized here.

In aortic insufficiency the pulse pressure is high, the diastolic is very low, even reaching 30 mm. Hg, and the fourth tone is frequently heard over the bare artery. A systolic pressure within the average normal range and a diastolic pressure of 50 mm. or below, should lead one to suspect aortic regurgitation.

In compensated true mitral insufficiency with enlarged left ventricle, the systolic pressure is usually in the upper zone of normal. In mitral stenosis the contrary condition is more apt to exist. The pressure falls in the lower zone of normal. In true aortic stenosis the systolic and diastolic pressures both show a rise. In decompensation the blood pressure estimation often gives us informa-

tion which auscultation over the heart or palpation of the radials fails to give. For example, the differences in the strength of individual beats are shown clearly, and the number of beats coming through at each mm. drop is distinctly heard. Any irregularities of rhythm are detected quickly when the cuff is on the arm.

A *pulsus alternans* is easily discovered by means of the auscultatory blood pressure phenomenon. In this condition the beats are alternately large and small, and the rate is regular. This is of great value in prognosis, as well as in diagnosis, when digitalis is being administered in large doses. It is one of the results of mild digitalis poisoning. *Pulsus alternans* is also a sign of serious myocardial insufficiency. It is not always possible to detect it by palpating the pulse. The regular heart may give the impression that all is well, but the blood pressure reading by the auscultatory method at once reveals the gravity of the patient's condition.

The Value of Blood Pressure Estimations.—No instrument, however precise, can serve for more than a part of a general examination. The sphygmomanometer is no exception to this rule. When used intelligently as a part of the physical examination, it has a distinct value and gives information which cannot be obtained in any other way. To expect the blood pressure instrument to establish the diagnosis is absurd. So much propaganda has been disseminated by the sales agents of sphygmomanometers that physicians have been led to believe that it is an instrument which will make diagnosis easy. When the estimations are at variance with the statement in the little booklets accompanying these instruments, the instrument is apt to be blamed rather than the variations in human beings. The routine use of the instrument is undoubtedly of great value. The majority of estimations on patients will be found to fall within the normal limits, but that should not cause the instrument to be discarded, as it is not at fault.

In fevers, in cardiac disease, in pregnancy, in renal disease, in asthenic states, in anesthesia, and in many other conditions, the estimation of the blood pressure at frequent intervals will be found to be most helpful in establishing a diagnosis and in assisting in the prognosis.

SELECTED BIBLIOGRAPHY

- ALLEN, E. V. AND BROWN, G. E.: Thrombo-anglitis obliterans of lower extremities with pulsating pedal arteries, *Am. J. M. Sc.*, 174: 329-337 (September) 1927.
- ALVAREZ, W. C., MCCALLA, R. L. AND ZIMMERMANN, A.: Hypertension and constipation; statistical inquiry, *Arch. Int. Med.*, 88: 158-166 (August 15) 1928.
- ALVAREZ, W. C. AND ZIMMERMANN, A.: Blood pressure in women as influenced by the sexual organs, *Arch. Int. Med.*, 37: 597 (May 15) 1926.
- BARACH, J. H.: *Arch. Int. Med.*, 24: 509 (November 15) 1919.
- BARNES, ARLEIE R. AND WHITTEN, MERRITT B.: Study of the R-T interval in myocardial infarction, *Am. Heart J.*, 5: 142 (December) 1929.
- BARRINGTON, T. B., JR.: *Arch. Int. Med.*, 17: 305 (March) 1916.
- BELL, E. T. AND CLAWSON, B. J.: Primary (essential) hypertension, *Arch. Path. & Lab. Med.*, 5: 939 (June) 1928.
- BLANKENHORN, M. A. AND CAMPBELL, H. E.: Effect of sleep on blood pressure, *Am. J. Physiol.*, 74: 115-120 (September) 1925 (Chart); Effect of sleep on normal and high blood pressure, *Am. Heart J.*, 1: 151-159 (December) 1925 (Chart).
- BOYER, G. AND THIBAUT, G.: Trophic troubles of vascular origin in thrombo-anglitis, *Presse méd.*, 35: 100 (January 22) 1927.
- BROWN, G. E. AND HENDERSON, M. S.: Diagnosis and treatment of arterial vascular disease of extremities in thrombo-anglitis obliterans, *J. Bone & Joint Surg.*, 9: 613-627 (October) 1927.
- CHRISTIAN, H. A.: Cardiac infarction coronary thrombosis: easily diagnosable condition, *Am. Heart J.*, 129-137 (December) 1925; *Northwest Med.*, 24: 601-605 (December) 1925.
- FAHR, K. T.: *Deutsche Arch. f. klin. Med.*, 134: 366, 1920.
- FISHBURG, A. M.: Anatomic findings in essential hypertension, *Arch. Int. Med.*, 35: 650-668 (May) 1925.
- : The arteriolar lesions of glomerulonephritis, *Arch. Int. Med.*, 40: 80 (July) 1927.
- FONTAINE, B. W.: Clinical study of end-results of some focal infections, *J. Am. M. Ass.*, 74: 1029 (June 12) 1920.
- GIRDWOOD, R. O.: Thrombo-anglitis obliterans, *J. Path. & Bact.*, 30: 643-646 (October) 1927.
- GOHRBANDT, P.: Importance for surgery in periarthritis nodosa, *Arch. f. klin. Chir.*, 145: 623-634, 1927.
- GUILLAUME, A. C.: A clinical study of thrombo-anglitis obliterans, *Gaz. d. hôp.*, 100: 1009 (July 30) 1927; 1041 (August 6) 1927.
- HAMMAN, L.: Symptoms of coronary occlusion, *Bull. Johns Hopkins Hosp.*, 38: 278-319 (April) 1926; Importance of embolic phenomena in diagnosis of coronary occlusion, *South. M. J.*, 20: 506-509 (July) 1927.

- HERRICK, J. B.: Thrombosis of coronary arteries, *J. Michigan M. Soc.*, 18: 49 (February) 1919; *J. Am. M. Ass.*, 72: 387 (February 8) 1919; *J. Am. M. Ass.*, 59: 2015, 1912 (many references given).
- KEITH, N. M.: Classification of hypertension and clinical differentiation of the malignant type, *Am. Heart J.*, 2: 597-608 (August) 1927.
- KEITH, N. M., WAGNER, H. P. AND KERNOHAN, J. W.: Syndrome of malignant hypertension, *Arch. Int. Med.*, 41: 141-188 (February 15) 1928.
- KIMMELSTIEL, P.: Pathology of periarteritis nodosa, *Virchow's Arch. f. path. Anat.*, 265: 16-80, 1927.
- LEVINE, S. A.: Coronary occlusion with recovery, *M. Clin. N. Amer.*, 8: 1719-1741 (May) 1925.
- LEVINE, S. A. AND STEVENS, W. B.: Therapeutic value of quinidine in coronary thrombosis complicated by ventricular tachycardia, *Am. Heart J.*, 3: 253-259 (February) 1928.
- LUTEN, DREW AND GROVE, EDWARD: The incidence and significance of electrocardiograms showing features of left axis deviation and QRS of normal duration with inverted T₁ and upright T₂, *Am. Heart J.*, 4: 431 (April) 1929.
- MAJOR, R. H.: Possible relationship between guanidine and high blood pressure, *Am. J. M. Sc.*, 170: 228-232 (August) 1925; Cause and treatment of arterial hypertension, *J. Kansas M. Soc.*, 25: 177-179 (June) 1925.
- MAJOR, R. H. AND STEPHENSON, W.: Effect of methyl guanidine on blood pressure, *Bull. Johns Hopkins Hosp.*, 85: 140-141 (May) 1924.
- MOORE, R. F.: Retinitis of arteriosclerosis, *Quart. J. Med.*, 10: 29 (October) 1916; (January) 1917.
- MURPHY, FRANCIS D. AND GRILL, JOHN: So-called malignant hypertension, *Arch. Int. Med.*, 46: 75 (July) 1930.
- O'HARE, J. P. AND WALKER, W. G.: Arteriosclerosis and hypertension, *Arch. Int. Med.*, 33: 843-849 (March 15) 1924.
- OHLEB, W. RICHARD: The signs and symptoms of hypertension, *Am. Heart J.*, 2: 609-612 (August) 1927.
- OPPENHEIMER, B. S. AND FISHER, A. M.: Association of hypertension with suprarenal tumors, *Arch. Int. Med.*, 34: 631-644 (November) 1924.
- PARDEE, H. E. B.: *Arch. Int. Med.*, 26: 244, 1920.
- PAULLIN, JAMES E., BOWCOCK, HAROLD M. AND WOOD, HUGH R.: Complications of hypertension, *Am. Heart J.*, 2: 613-617 (August) 1927.
- POLAK, J. O., MITTELL, E. A. AND MCGRATH, A. B.: What is the relation of hypertension to fibroid disease of uterus? *Am. J. Obst. & Gynec.*, 4: 227-233 (September) 1922.
- SCALA, G.: Periarteritis nodosa in man and in animals, *Folia med.*, 13: 1170-1175 (August 30) 1927.
- SCOTT, R. W.: Syphilitic aortic insufficiency, *Arch. Int. Med.*, 34: 645-657 (November) 1924.
- SCOTT, R. W. AND SAPHIR, O.: Involvement of aortic valve in syphilitic aortitis, *Am. J. Path.*, 8: 527-536 (September) 1927.
- SEWALL, H.: *Am. J. M. Sc.*, 158: 786 (December) 1919.
- SILBERT, S.: Effectiveness of therapeutic procedure in thrombo-angitis obliterans, *J. Am. M. Ass.*, 89: 964-966 (September 17) 1927.
- SINGER, H. A.: Report of two cases of periarteritis with special reference to acute abdominal manifestations, *Arch. Int. Med.*, 39: 863-889 (June) 1927.
- SMITH, F. M.: Electrocardiographic changes following occlusion of left coronary artery, *Arch. Int. Med.*, 32: 497-509 (October) 1923; *Arch. Int. Med.*, 22: 8, 1918.
- SMITH, F. M. AND GRABER, V. C.: Coronary thrombosis with congenital absence of left coronary artery, *Arch. Int. Med.*, 38: 222-225 (August) 1926.
- STEEL, W. A.: Clinical aspect in thrombo-angitis obliterans, *Internat. Clin.*, 3: 46-51 (September) 1927.
- STIEGLITZ, EDWARD J.: Arterial hypertension, evaluation of prognosis, *Arch. Int. Med.*, 46: 227 (August) 1930.
- TELFORD, E. D. AND STOPFORD, J. S. B.: Two cases of thrombo-angitis in women, *Brit. M. J.*, 1: 1140-1141 (June 25) 1927.
- TERRY, A. H.: Obesity and hypertension, *J. Am. M. Ass.*, 81: 1283-1284 (October 13) 1923.
- : Various articles in symposium on syphilitic aortitis, *Am. Heart J.*, 6: 1-162 (October) 1930.
- VOLHARD, FRANZ AND FAHR, K. T.: *Die Brightsche Nieren-Krankheit*, Julius Springer, Berlin, 1914.
- WARFIELD, L. M.: Studies in auscultatory blood pressure phenomena, *Arch. Int. Med.*, 10: 258-267 (September) 1912; Pulse pressure, *J. Am. M. Ass.*, 68: 824 (March 17) 1917; Chronic high blood pressure, *Am. J. M. Sc.*, 154: 414 (September) 1917; Etiology of arteriosclerosis, *J. Lab. & Clin. Med.*, 8: 115 (November) 1917; Classification of high blood pressure cases, *Wisconsin M. J.*, 16: 200 (November) 1917; Present status of blood pressure, *Internat. Clinics*, 4: 93, 1919; Cardiovascular-renal syndrome, vascular aspect, *Ann. Clin. Med.*, 2: 223-230 (January) 1924; Prognosis in chronic hypertension, *Wisconsin M. J.*, 26: 6-15 (January) 1927.
- WARTHIN, A. S.: Syphilis of medium and smaller arteries, *New York M. J.*, 115: 69-73 (January 18) 1922.
- WARTHIN, A. S. AND OTHERS: Clinical pathological conference; cases illustrating right ventricular preponderance; Ayerza's disease with atherosclerosis and syphilis of pulmonary arteries; mitral stenosis with and without free ball thrombus; rupture of syphilitic aneurism of aorta; angina pectoris with coronary atherosclerosis and thrombosis and sympathectomy, *Ann. Clin. Med.*, 5: 9-56 (July) 1926.
- WEARN, J. T.: Thrombosis of coronary arteries, *Am. J. M. Sc.*, 165: 250-276 (February) 1923.
- WHITE, P. D.: Prognosis of angina pectoris and of coronary thrombosis, *J. Am. M. Ass.*, 87: 1525-1530 (November 6) 1926.
- WHITNEY, J. L.: Studies in aviation. III. Cardiovascular observations. *J. Am. M. Ass.*, 71: 1889 (October 26) 1918.

CHAPTER II

ACUTE ENDOCARDITIS

By FREDERICK TICE, M.D., F.A.C.P.

Definition, p. 63.

Acute simple endocarditis, p. 64—Definition, p. 64—Synonyms, p. 64—Etiology, p. 64—Essential cause, p. 64—Associated diseases, p. 64—Predisposing causes, p. 65—Age, p. 65—Sex, p. 65—Pathology, p. 65—Pathogenesis, p. 66—Symptomatology, p. 67—Physical signs, p. 68—Laboratory findings, p. 68—Differential diagnosis, p. 69—Complications, p. 69—Course of the disease, p. 69—Treatment, p. 69—Prognosis, p. 70.

Acute infective endocarditis, p. 71—Definition, p. 71—Synonyms, p. 71—Etiology, p. 71—Essential cause, p. 71—Associated diseases, p. 71—Pathology, p. 71—Clinical varieties, p. 72.—The septicopyemic form, p. 72—The typhoid form, p. 73—Cerebral form, p. 73—Differential diagnosis, p. 73—Sepsis and septicopyemia from any cause, p. 74—Typhoid fever, p. 74—Meningitis, p. 74—Malaria, p. 74—Prognosis, p. 75.

Subacute bacterial endocarditis, p. 75—Definition, p. 75—Synonyms, p. 76—Etiology, p. 76—Essential cause, p. 76—Predisposing causes, p. 77—Pathology, p. 79—Symptomatology, p. 80—Onset, p. 81—The fever, chills and sweats, p. 81—Cutaneous and mucous membrane manifestations, p. 82—Cardiac manifestations, p. 83—The blood, p. 83—Vascular lesions, p. 84—Genito-urinary manifestations, p. 85—Cerebrospinal manifestations, p. 85—Gastro-intestinal and abdominal manifestations, p. 85—The clinical course, duration and mode of termination, p. 86—Diagnosis, p. 86—Differential diagnosis, p. 87—Treatment, p. 88—Prognosis, p. 90.

Definition.—Endocarditis signifies an inflammation of the lining membrane of the heart, oftentimes peculiarly limited to the valves of the heart, when the term valvulitis may appropriately be applied. In some instances the lesion is relatively slight, limited to a single valvular cusp, to a small area of the mural endocardium, to a papillary muscle, or the lesion is only a part of an extensive involvement of the entire heart, a pancarditis, in which the predominating symptoms and signs may be endocardial, myocardial or pericardial.

From an anatomic and clinical consideration it is possible to subdivide endocarditis into acute, subacute and chronic. Acute and subacute endocarditis is characterized by the presence of vegetations, with or without destruction of the endocardial tissue; while the chronic consists of a sclerotic process, producing a thickening and deformity, which leads to some form of chronic valvular disease. It is the end-result of a previous inflammatory process, and, while designated as chronic endocarditis, it really is a sclerosis or fibrosis. Not infrequently the damaged leaflets predispose to an acute reinfection, producing a recurrent or subacute type of endocarditis.

Acute endocarditis, due to some form of infection, may also be subdivided into two types, the simple or benign and the bacterial, infective, ulcerative or malignant.

The statement has been made that the two types are clinical manifestations of a difference in the virulence of the etiologic factor, combined with a varying local or systemic immunity reaction. This can hardly be accepted, except perhaps in unusual instances, as the bacterial factor, the pathology and even the clinical manifestations are so widely different as to constitute almost a different disease.

ACUTE SIMPLE ENDOCARDITIS

Definition.—Acute simple endocarditis is an infection of the lining membrane of the heart, usually limited to the valves, characterized anatomically by the presence of small vegetations and etiologically, in most instances, associated with acute rheumatic fever.

Synonyms.—*Acute simple endocarditis; benign endocarditis; verrucous endocarditis; rheumatic endocarditis; mild infective endocarditis.*

This form is by all means the most frequent, practically never occurring as a primary, independent disease but secondary to some previous local or systemic infection.

Etiology.—**ESSENTIAL CAUSE.**—This consists of some form of bacterial infection, which becomes localized in or on the endocardium during the course of or following some previous disease. The following bacteria have been described and considered as the essential cause in this form of endocarditis: *Micrococcus* or *Diplococcus rheumaticus* of Poynton and Paine, streptococcus of some type, staphylococcus, pneumococcus, bacilli of typhoid, tuberculosis and diphtheria, colon bacillus and a few others less frequent and important.

ASSOCIATED DISEASES.—(a) Rheumatic arthritis, including tonsillitis and chorea, as probably due to the same type of infection, is responsible for 25 to 90 per cent of this form of endocarditis. The relationship between acute rheumatism and endocarditis was suspected by Baillie, mentioned by Kreisig and later demonstrated by Bouillaud, who coined the term *endocarditis* and also called attention to the frequent association of valvular disease with other acute infections. While acute rheumatism was suspected as the cause of endocarditis, it remained doubtful until Bouillaud enunciated his famous laws, which were, briefly stated, as follows:

1. That in acute articular rheumatism of a violent type and general distribution, the coincidence of pericarditis and endocarditis is the rule, and the noncoincidence the exception.

2. That in acute articular rheumatism of a mild type and partial distribution, the noncoincidence is the rule, and the coincidence the exception.

Bouillaud and Trousseau also observed that the endocarditis might antedate the articular manifestations, reversing the usual clinical course.

All observers are now convinced of the etiologic importance of acute rheumatism in acute endocarditis.

Probably nearly all are also convinced that the essential factor is bacterial, but there is not the same convincing proof of the specific type of the organisms, although there is acceptable evidence in favor of the *Micrococcus rheumaticus*. There seems to be some doubt as to the specificity of the organism as well as its relation to some forms of the streptococcus.

Ample and abundant statistics as to the frequent association of acute rheumatism and endocarditis may be found, only a few of which will be quoted. Osler found acute endocarditis in 33 per cent; Fagg 50 to 55 per cent; Latham and Sibson 66 per cent. According to Norris, 80 to 90 per cent of simple, benign endocarditis is rheumatic in origin. Osler reports autopsy findings of endocarditis in 84 per cent of his fatal cases of chorea.

The percentage in tonsillitis is not easily estimated as it is so frequently associated with an arthritis, and in many cases, especially in children, the disease occurs without recognition.

(b) Some of the eruptive fevers, as scarlet fever, measles, chickenpox and smallpox, may be considered as an occasional cause. Most important of the group is scarlet fever, especially when accompanied by an arthritis.

(c) Diphtheria, pneumonia and typhoid fever may be complicated with endocarditis.

(d) Chronic diseases associated with anemia and loss of weight, as phthisis, carcinoma, gout, diabetes and chronic nephritis, frequently reveal at autopsy a few or moderate numbers of vegetations on the endocardium.

(e) Arteriosclerosis with atheroma of the aorta and degenerative sclerosis of the valves may be the seat of a terminal infection.

PREDISPOSING CAUSES.—Age.—Rheumatic endocarditis is far more frequent in children, according to Holt, 90 per cent occurring between the ages of five and fourteen years. According to the same author, also Pisek and Lovett, as well as others, 90 per cent in children is associated with tonsillitis, rheumatism and chorea, while in older patients the percentage drops to 60 per cent. It is in children that tonsillitis may occur unrecognized and rheumatic manifestations consist only of so-called "growing pains." The heart lesion may be the first evidence of a rheumatic infection.

Sex.—According to some writers, males are more prone to develop endocardial complications, but it is difficult to understand why this should be, particularly in children. Perhaps in the adult there may be some contributing factor due to occupation, habits and mode of life.

Pathology.—The characteristic lesion consists of minute vegetations from 1 to 4 mm. in diameter, situated on the lining membrane of the valves, the papillary muscles or the chambers of the heart. The surface of the vegetations is rough, irregular and attached by a broad base or pedunculated. In appearance they resemble a warty or cauliflower excrescence.

There may be but a very few, and these small in size, or they may be numerous and sometimes grouped together into a considerable-sized

mass. They are more common in the left heart and more numerous on the mitral than the aortic leaflets. They are usually situated, not at the edge of the valves, but just back of the line of contact, on the auricular surface of the auriculoventricular valves and the ventricular surface of the sigmoids. There is no evidence of inflammatory reaction and no tendency to destruction or ulceration.

The future course of the vegetations depends on the type and virulence of the infection as well as the local or general resistance.

In the larger number of cases the vegetations undergo organization and partially or completely disappear, but they are responsible for initiating a nutritive change resulting in a sclerosis of the valvular substance, which leads to a chronic valvular lesion. In a small percentage the simple, benign form is merged into a more active, malignant and infective type.

Rarely a vegetation becomes detached and forms an embolus, or, even less frequently, the vegetation is organized, disappears and the valve restored to normal.

Practically all clinicians are agreed that the mitral leaflets are most frequently involved, and autopsy records confirm this, revealing that the mitral lesions occur twice as often as the aortic, then, next in order of frequency, the aortic, the tricuspid and the pulmonary.

As all forms of acute endocarditis are associated with focal or systemic infection in which the endocardium becomes secondarily infected, it may be advantageous at this time to discuss the mode of infection and the resulting anatomic changes.

Pathogenesis.—The earlier conception that acute endocarditis was bacterial in origin was apparently first confirmed by Winge, and substantiated by Heiberg, Köster and Klebs. More recently the work of Weichselbaum, Osler, Frankel, Sanger, Rosenow and many others has placed the bacterial basis beyond question and has also advanced our knowledge in other respects.

The first and primary essential, then, is some form of disease with a systemic infection. The next problem is the route or mode of infection of the endocardium. There are two contending views. Klebs advanced the opinion that the bacteria in the circulating blood simply settles on the surface of the leaflets and produces the anatomic changes. Köster, on the contrary, was of the opinion that the bacteria are carried to the substance of the leaflets by means of their own vascular supply, producing valvular bacterial emboli. This opinion or suggestion was vigorously opposed on the basis that little or no valvular vessels could be demonstrated. Since that time this objection has been completely eradicated by the thorough study of the blood supply of the heart by Louis Gross and others.

Rosenbach and Wyssokowitsch were unable to produce an endocarditis by wounding the valves by means of a sterile instrument. However, the latter observer, after traumatic injury of the endocardium and injecting streptococci and staphylococci, produced experimental endocarditis. The observations of Ribbert are of considerable importance, as he was able to

produce endocardial lesions by injecting staphylococci without previous injury to the valves. Presumably the culture was sufficiently virulent, or the toxins present produced sufficient damage to the lining membrane to permit an invasion and resulting infection.

The more recent work of Rosenow is most illuminating and instructive. The first lesion produced in experimental endocarditis consists of a subendocardial hemorrhage in the substance of the mitral leaflets. This is followed by a proliferation of the subendothelial and endothelial cells, with a deposition of blood platelets, fibrin and leukocytes. The vegetations thus formed, partly by cellular proliferation and partly by depositions from the blood, practically always contain the exciting organism. Later absorption and fibrosis may occur or the process becomes more extensive, perhaps with ulceration and destruction. Involvement of the aortic leaflets may be by direct extension or they become embolized and analogous to the method in the mitral valves.

Having considered the etiologic cause of endocarditis and the mode of infection of the endocardium, it still remains necessary to refer to the probable factors which influence the location of the infection in the mitral leaflets and to determine why endocardial infections are so much more prevalent in childhood and early life. It would seem that the anatomic observations of Louis Gross, previously referred to, are more than ample and convincing. According to his findings the fetal valves are supplied with a musculature and blood vessels which undergo a regression after birth, persisting longer in the aortic cusp of the mitral valve, where endocarditis is most frequently found. Attention is also directed to the occurrence of periodic compression of the valvular vessels, a peculiarity that does not occur in any other organ of the body. According to Howell, in every 24 hours the capillaries in the auriculoventricular valves are compressed 10.6 hours and the semilunar valves 13.5 hours.

It would seem that the greater vascular supply at different ages and its greater amount in the mitral leaflets, combined with the constant interference of blood flow, favoring localization of the bacteria, logically explain the greater incidence of endocarditis in early life and why the mitral valves are the site of predilection.

Symptomatology.—The clinical symptoms and physical signs of an acute simple endocarditis are by no means characteristic. The clinical manifestations of the primary disease may be so evident as completely to dominate the clinical picture. Occurring in the course of some other acute disease, usually rheumatic fever, there may be no cardiac symptoms or signs suggesting an endocardial complication. Valvular vegetations, as a terminal complication, are a comparatively frequent autopsy finding in many of the chronic wasting diseases. If the patient is under constant clinical observation certain symptoms and signs may occur that should arouse suspicion and lead to a careful examination.

During or following especially an attack of acute rheumatic fever, the symptoms of significance consist of palpitation, increased rapidity of the heart, perhaps a disturbed rhythm and an increase in the fever, not

to be accounted for by the arthritis. According to many competent observers, the appearance of palpitation is considered very important. The small, almost insignificant vegetations hardly seem capable of producing a pyrexia, but clinical and autopsy study reveals abundant incriminating evidence. As a rule there is no cardiac pain unless there is some existing complication.

PHYSICAL SIGNS.—The diagnosis depends upon the physical signs, which are as uncertain as the symptoms. Vegetations may occur without producing any symptoms and absolutely no change in the physical findings. Perhaps the most frequent finding suggestive of possible endocarditis is an apical systolic murmur. At first the systolic tone is slightly muffled, then gradually merges into a definite murmur; but to make this the proof of the existence of an endocarditis is anything but precision. Frequently the murmur is due to an accompanying myocarditis, with dilatation of the valvular orifice, or perhaps to an associated anemia.

Unquestionably, a few of the cases interpreted as myocardial or hemic may be due to a mild evanescent infection and promptly clear up. It may be safely stated that the presence of a systolic murmur, regardless of its intensity or quality, is far short of being a pathognomonic diagnostic criterion.

More dependence can be placed on the form of the murmur, and perhaps of some value is the relative time of its development. With only few exceptions, the diastolic and presystolic murmurs are associated with organic cardiac lesions. The presence of a double murmur at the apex, or a diastolic over the aortic area, developed during the course of an acute infection, may be accepted as significant of complicating endocardial disease.

As to the time element, Gibson is of the opinion that the systolic murmur appearing with the first attack of rheumatism is endocardial in origin. Samson emphasizes the greater importance of the period of time which elapses between the onset of the primary infection and the appearance of the murmur. According to his observation, a relatively short period signifies endocardial involvement, while a longer period is required for a myocardial complication, with relaxation and a murmur.

LABORATORY FINDINGS.—In this form of endocarditis the absence of definite findings is more significant than otherwise.

Blood examination usually reveals the findings that might be anticipated in the primary disease. Secondary anemia is quite the rule.

Blood and urinary cultures, so important in the acute infective type of the disease, are usually negative and assume diagnostic importance on that account.

The formaldehyde gel test of Kürten, while advocated and employed as a possible differential diagnostic procedure in endocarditis, may also be applied as a means of direct diagnosis.

Electrocardiograms can be of only indirect service by revealing the presence of an arrhythmia or rheumatic myocarditis and, by inference, assigning the murmur to a complicating myocarditis.

Differential Diagnosis.—Having accomplished the difficult problem of establishing the existence of an acute endocarditis, diagnostic accuracy requires that the particular type be determined, as upon this will depend the clinical course and prognosis. One of the most important considerations is the clinical differentiation between the rheumatic endocarditis, the acute infective and the subacute, which can be more advantageously discussed later.

Complications.—These may be cardiac or otherwise. The most frequent associated pathologic changes, as previously mentioned, consist of an acute myocarditis, a pericarditis, or both. In some instances it may be a question as to whether the endocarditis is primary or constitutes the complication.

Acute pleurisy, plastic or serofibrinous, is occasionally found. So-called rheumatic pneumonia, when present, is due to some other type of infection. Clinical evidence of the primary etiologic disease, acute rheumatic fever, tonsillitis, chorea or some other disease may be present.

In this form of the disease, emboli are very infrequent but occasionally occur, producing symptoms and signs depending upon the localization.

Course of the Disease.—This will depend upon the type of the infection, the immunity reaction and the existing associated pathology. In some instances there is a complete symptomatic recovery, but, in the greater number, after apparent recovery or decided improvement, there gradually develop the symptoms and signs of a chronic valvular lesion. In infants and children the disease may assume a comparatively severe and progressive course, going on to a fatal termination. The manifestations may be so pronounced as to suggest or even justify the diagnosis of an acute infective endocarditis.

Treatment.—The ideal to be attained is the prevention of endocardial infection, particularly in the diseases with which it is most frequently associated. Unfortunately there is no known drug or laboratory product capable of accomplishing this most desired result.

Much, however, may be done to lessen the danger, and perhaps minimize the lesion by instituting and maintaining **physical rest** during the clinical course of certain diseases, especially the rheumatic group of infections. Sibson has demonstrated, both experimentally and clinically, the importance of rest as a preventive measure. Absolute rest in bed for weeks or months, maintained with difficulty in children and against protests and objections in adults, may accomplish much more than all the drug therapy. If the heart is rapid or palpitation is present, an **ice-bag or cold water coil** is a valuable adjunct.

Physical rest comes to the relief of the heart in various ways. With the rest there is a slowing of the heart rate, which allows more physiologic rest, with a more efficient systolic contraction and improved nutrition of the entire heart.

Slowing the heart rate only one beat a minute means 1,440 less contractions in twenty-four hours, or 14,400 if there is a decrease of ten beats per minute, which must have a beneficial effect in decreasing the mechanical influence producing local valvular injury and infection.

As the rheumatic group of infections is the most frequent etiologic factor, **suitable and appropriate drug therapy** should be instituted. According to some observers there would seem to be a question as to the harmful effect of the various salicylic compounds on the endocardium. Nevertheless, they have attained a considerable reputation in the treatment of acute rheumatic fever with arthritis.

The choice of the preparations and the dosage are partially an individual question. **Sodium salicylate**, in combination with **sodium bicarbonate**, of each 5–10 gr. (0.324–0.65 gm.), is a favorite combination. If the attack is acute, the salicylate and bicarbonate should be given every hour, with abundance of **water, hot lemonade or orangeade**, for the first twelve to twenty-four hours, after which time the frequency may be lessened. The more active the treatment, the better the results and naturally the less the danger of heart involvement.

Abundance of fluids is important and necessary, as well as efficient and thorough **elimination by the kidneys and bowels**. Some clinicians prefer **acetylsalicylic acid**, 5–10 gr. (0.324–0.65 gm.), every three or four hours, while others prefer **strontium salicylate**, **salicin** or the **sodium salicylate** made from the natural wintergreen oil, as less likely to produce a tinnitus or a gastric upset. Because of the harmful effect of the secondary anemia upon the nutrition of the myocardium and because it is often progressive in type, **combative measures** should be employed. **Sunshine, a suitable diet**, with some form of **iron** by mouth or subcutaneously, and **liver extract**, preferably the hypodermic form, for secondary anemia, are all worthy of trial.

Perhaps a diuretic may be required, in which event some one of the theobromine compounds is usually employed, such as **diuretin**, 10 gr. (0.65 gm.); **theocin** or **theocalcin**, 5 gr. (0.324 gm.), while **potassium acetate**, **potassium citrate** or **potassium bitartrate**, 10–30 gr. (0.65–1.95 gm.) are quite dependable.

As to **digitalis**, there is a wide difference of opinion as to the necessity and, furthermore, as to the advisability of its use. It is probably true that the greater number of cases do not require digitalis, but when there is evidence of disturbed compensation it should be given in small or moderate doses and increased as required. Any dependable preparation for oral or hypodermic administration can be used, but, if the indications are urgent, the intravenous route is the one of choice.

In an emergency, **cafein sodium benzoate**, 3 gr. (0.195 gm.), **camphor in oil**, 3 gr. (0.195 gm.), given hypodermically at frequent intervals, or **strychnia sulphate**, 1/60–1/30 gr. (0.001–0.002 gm.), hypodermically every three or four hours, is occasionally of service.

Prognosis.—The acute simple endocarditis rarely ever is fatal. The danger is not immediate but remote, due to the nutritive changes initiated and the resulting fibrosis of the leaflets and papillary muscles, producing valvular lesions and finally cardiac decompensation. Generally speaking, when the lesion is a simple mitral regurgitation and is not excessive in degree, the prognosis is relatively good. When the lesion is a double mitral regurgitation and stenosis combined, the latter usu-

ally is progressive and associated with additional danger. Aortic lesions, especially regurgitation, carry with them the danger of acute cardiac failure or decompensation from lack of efficient compensation.

It must not be forgotten that the estimated prognosis does not depend alone on the form of the valvular lesion or the degree of involvement. The presence or absence of a complicating myocarditis is all-important. As long as the myocardium remains intact, compensation is usually maintained regardless of the valvular mechanical imperfection.

ACUTE INFECTIVE ENDOCARDITIS

Definition.—Acute infective endocarditis, like the acute simple form, is an infection of the lining membrane of the heart, characterized anatomically by the presence of vegetations, with a marked tendency to destruction and loss of continuity of the valvular and myocardial structure, due to some form of bacterial infection.

Synonyms.—*Acute infective endocarditis; ulcerative endocarditis; malignant endocarditis; bacterial endocarditis; thrombo-ulcerative endocarditis.*

This form of endocarditis is, comparatively, not as frequent as the form just described. It may occur as (a) primary infection of the endocardium or (b) secondary to some acute, local or systemic disease.

Etiology.—**ESSENTIAL CAUSE.**—Bacterial infection is always present, including most frequently the pneumococcus, streptococcus, gonococcus, staphylococcus, and less frequently the bacillus of diphtheria and typhoid and occasionally the meningococcus.

ASSOCIATED DISEASES.—(a) Lobar pneumonia probably heads the list. In Kanthack's series there was an antecedent pneumonia in 14.2 per cent; in Osler's 209 collected cases of acute infective endocarditis, 54 occurred in pneumonia. In the often-quoted 517 fatal cases of Wells, 22.3 per cent were in pneumonia.

(b) As a close second to pneumonia must be mentioned puerperal fever, general sepsis, septicopyemia and focal infections due to the streptococcus or staphylococcus. In a given series of cases, occurring at a period when pneumonia is not prevalent, the pyogenic may exceed the pneumococcal.

(c) Gonorrhea, with its complications, is a not infrequent associated cause.

(d) The rheumatic infections may rarely cause the acute infective form. When this occurs, it is acute and active from the inception. The acute simple rarely, if ever, merges into the acute infective form.

(e) Influenza is held responsible by some observers as a cause. In view of our present unsettled knowledge of the bacteriology of this disease, the advisability of including it as an etiologic factor is questionable.

Pathology.—In most instances infective endocarditis is a systemic infection and the endocarditis is only one of the local manifestations. The pathogenesis is exactly the same as previously described, either an embolic or direct infection of the endocardium, with certain areas of predilection. As in the acute simple endocarditis, the mitral leaflets are

most frequently involved, with a definite tendency to multiple valvular lesions, as well as the mural lining of the heart. Certain organisms, notably the pneumococcus but especially the gonococcus, manifest a selective election to involve the aortic valves. In any variety of infection, in this particular form, the thrombus formation and the destructive tendency are much more pronounced, along with a greater abundance of the organisms and a corresponding increase of virulence. The destructive, ulcerative process may be limited to the superficial surface of the endocardium but more frequently extends to the deeper structures, resulting in a perforation of a leaflet, the septum or wall of the heart. Not infrequently an entire leaflet is destroyed or one of the papillary muscles is severed. Careful examination fails to reveal any microscopic evidence of inflammatory infiltration or ulceration, as observed in the ordinary wound infection. Almost without exception there is gross and microscopic evidence of a previous sclerotic endocarditis, which is evidently one of the potent predisposing factors to a reinfection. According to some observers the sclerotic endocarditis results in an increased vascularity of the valves, while others maintain that the fibrosis decreases the vascular supply. Whether it is one or the other, there is evidently a lowered resistance and predisposition to infection.

The occurrence of emboli, consisting of bacteria, portions of vegetations of fibrin, with resulting infarcts, produces a varied and mixed variety of pathologic changes, depending upon the number and location of the emboli.

Myocarditis and pericarditis are not infrequent, due to extension or the result of the primary infection.

Clinical Varieties.—To give a clear, concise clinical picture of acute infective endocarditis is impossible. The disease is protean in its mode of onset, symptomatic manifestations and clinical course. The best that can be done is to attempt a description of the various clinical varieties or forms.

THE SEPTICOPYEMIC FORM.—As the name implies, the onset is ushered in with the usual symptoms of an infection. Not infrequently, without evidence of a previous disease, there may be chills, fever and drenching sweats. The pyrexia is usually of the septic, irregular type, depending on the previous disease and the form of the infection. Sometimes the initial symptoms consist of a backache, hematuria and urinary evidence of a renal infection, to be followed later by cardiac signs of heart disease. The occurrence of emboli produces a varied clinical phenomenon and often constitutes the first suggestive evidence of endocarditis. There may be a single embolus, but multiple emboli are the rule. They become localized in the spleen, kidney, brain, mesentery, peripheral vessels, retina, skin and mucous membranes. The spleen is usually palpable, enlarged from the septic infection or more frequently from emboli and infarction. Tenderness on palpation and a friction rub on auscultation, due to a perisplenitis, can frequently be found.

The skin and mucous membrane lesions vary from small petechial hemorrhages to areas of purpura or large ecchymoses.

A delirium, coma, a hemiplegia or perhaps a meningitis are some of the cerebral manifestations, which may be due to the infective toxemia or to a cerebral embolus but, far more frequently, are due to an encephalitis, which is a part of the general infection of which the endocarditis is only a part.

THE TYPHOID FORM.—There may be no history of a previous infection, as in the preceding form, but the onset is slow and insidious. The patient complains of a general malaise, headache, perhaps slight chills and fever, abdominal distress with diarrhea. The spleen may be enlarged, petechiae appear, there is a gradually developing cerebral stupor or low muttering delirium with a subsultus tendinum, all of which are strongly suggestive of typhoid fever; particularly so if the heart presents little or no convincing evidence of disease.

CEREBRAL FORM.—The mode of onset and the symptoms suggest a meningitis or some cerebral disease. Headache, nausea, vomiting, an aphasia, delirium, coma or some form of psychosis dominates the clinical picture.

The aphasia and hemiplegia, as well as the secondary meningitis due to an infected cerebral embolus, should be sufficient to arouse suspicion of the existence of an acute endocarditis. Many of the symptoms enumerated as belonging to this form are undoubtedly due to an encephalitis or a meningo-encephalitis.

Other forms have been described as belonging to the group of acute infective endocarditis, but they present no distinguishing feature to justify a separate consideration.

The diagnosis in all three forms must depend upon the physical and laboratory findings. As previously stated, the most careful and exacting examination of the heart may fail to reveal any evidence whatever. There are no murmur, no change in the heart tones and no enlargement on percussion. Nevertheless, the autopsy reveals an acute infective endocarditis, so situated on the endocardium as to be incapable of producing physical signs. The comments on the significance of the various murmurs in the acute simple endocarditis might be repeated here with equal force.

Blood cultures are most important and significant but are not to be accepted as pathognomonic, for a general sepsis may give a positive culture where no endocardial complication has occurred.

Positive cultures, depending upon many factors, may be obtained in 60 to 80 per cent of the cases. Occasionally cultures of the urine, obtained by catheterization, will be positive even when those from the blood remain negative.

Blood examination usually reveals the typical findings of a secondary anemia, with a leukocytosis and a predominating polymorphonuclear differential.

Differential Diagnosis.—It must be constantly born in mind that the clinical problem consists in determining whether or not the endocardium has become infected in the course of some one of the possible etiologic diseases, rather than differentiating an endocarditis from that particular

disease which it may simulate. Some of the diseases requiring consideration should be mentioned.

SEPSIS AND SEPTICOPYEMIA FROM ANY CAUSE.—As long as the heart remains normal, although the cultures, both blood and urine, are positive, there is no necessity to consider seriously a differential determination. This is particularly true if there is convincing proof of a sepsis or pyemia the result of a puerperal fever, a surgical sepsis or some focal infection. When the cardiac findings are definite and convincing proof of an endocarditis, associated with symptoms of a sepsis or pyemia, it becomes necessary to determine the presence or absence of a primary disease.

TYPHOID FEVER.—Here the task is comparatively simple. The fever in typhoid is more constant and may present the step-like onset; the cultures, early in the disease, or the Widal, after the first week or ten days, will decide the problem at once. The leukopenia, with a relative increase of the mononuclears, is always suggestive but not decisive.

MENINGITIS.—Physical findings may be insufficient, but a lumbar puncture will usually yield diagnostic evidence. As previously stated, a coexisting or complicating encephalitis is by no means infrequent.

MALARIA.—In those cases with recurrent chills, fever and sweats, associated with an enlarged spleen, it is easy to conceive of the bedside difficulty in arriving at a differential diagnosis, without any laboratory assistance. Microscopic examination of the fresh or stained blood smears will usually reveal a ready diagnosis.

Having determined the presence of an acute endocarditis, it still remains necessary to differentiate between the acute simple endocarditis and the acute infective endocarditis. The following considerations may be of service:

- (a) Possible etiologic factor: Rheumatic fever, chorea, tonsillitis and scarlet fever are usually associated with the acute simple or rheumatic form, while the acute infective form is associated with a pneumonia, septicopyemia or gonorrhea.
- (b) Character of the fever: In the rheumatic form the pyrexia is only slight or perhaps entirely absent, but in the acute infective it is pronounced, of the intermittent, recurrent or septic type, and sometimes associated with chills.
- (c) While a single embolus may occasionally occur in the rheumatic form, multiple emboli at once suggest the infective form.
- (d) Petechiae and hemorrhages into the skin and mucous membranes are usually limited to the infective form.
- (e) The same may be said of the enlarged, palpable spleen.
- (f) Negative blood and urine cultures are the rule in the rheumatic form, but in the infective they are usually positive, depending on a number of factors.
- (g) The rheumatic form occurs more frequently early in life and is responsible for the greater prevalence of endocarditis in children.

- (h) The mitral leaflets are the site of election in a rheumatic infection, while the pneumococcus and gonococcus by preference attack the aortic valves.
- (i) As previously stated, the rheumatic endocarditis is frequently associated with a myocarditis or myocarditis and pericarditis. Aschoff bodies occur in practically 100 per cent of the acute rheumatic infections but are not pathognomonic, for identical bodies have been described by R. H. Jaffé in scarlet fever. The infective form no doubt tends to a similar complication but it is far less evident.
- (j) The formaldehyde gel test of Kürten is of differential assistance but unfortunately may occur in other conditions. The test consists of adding one drop of neutral formalin to 1 cc. of blood serum, then setting the solution aside for twenty-four hours, at the end of which time the serum of a bacterial endocarditis should solidify but fails to do so in the rheumatic endocarditis.
- (k) Rheumatic endocarditis usually pursues a more mild clinical course and terminates in a chronic valvular fibrosis, although in some instances there is a relatively rapid and unfavorable outcome, due to the failing myocardium. The infective form runs a more progressive and unfavorable course from the onset.

Prognosis.—Most of the cases have a fatal termination; a recovery is the exception. The clinical course and termination are determined by the type of the infection and the degree of the local and systemic immunity. Infections with the pneumococcus, *Streptococcus haemolyticus* and the *Staphylococcus aureus* are particularly acute, with a rapid and fatal course. Those due to the gonococcus and *Staphylococcus albus* are somewhat less acute, and while quite equally destructive, the clinical course is more prolonged, with an occasional recovery.

Judging from the appearance of the endocardial lesion, both gross and microscopic, there apparently is little local resistance to the infection. Even the systemic resistance, considering the high mortality, must be low and ineffectual to limit or combat the infection. This is particularly evident in the cases with a rapid course, considerable toxemia as manifest by the septic fever, a rapidly developing anemia and a low leukocyte count. The immunity mechanism apparently is paralyzed by the virulence of the infecting organism.

The duration of the clinical course is quite variable. Eberth has recorded one case in which the duration was a little less than forty-eight hours. A fair average is from five or six weeks to three or four months, while a few may exceed this time limit for a few additional weeks or months.

SUBACUTE BACTERIAL ENDOCARDITIS

Definition.—Subacute bacterial endocarditis is characterized anatomically by an infection of the endocardium and etiologically by the presence of the *Streptococcus viridans*, while the clinical course is relatively prolonged with various phenomena.

Synonyms.—*Subacute bacterial endocarditis* (Libman); *subacute infective endocarditis* (Libman and Celler); *chronic septicemic endocarditis* (Riesman); *endocarditis lenta* (Schottmüller); *endocarditis septica lenta* (Lossen); *endocarditis maligna a decorso lento* (Italian School); *endocarditi a forma infectiva prolongata* (Vaquez).

Etiology.—**ESSENTIAL CAUSE.**—This, as the name implies is bacterial and, according to Schottmüller, Libman, Horder and others, there are practically only two organisms concerned in subacute bacterial endocarditis, the *Streptococcus viridans*, which causes, according to Libman, 95 per cent of the cases, and the *Bacillus influenzae*, which is responsible for the remaining 5 per cent. Our present knowledge of the latter organism is so chaotic and uncertain that it would seem permissible and advisable to limit the bacterial etiology to a single specific organism.

The *Streptococcus viridans* was first described by Schottmüller, designating it as the *Streptococcus mitior seu viridans*. Litten named it *Streptococcus gracilis* and Lenhart used the term *Streptococcus parvus*, or small streptococcus. It is probably identical with the *Streptococcus der Schleimhäuten* of Kruse, the saprophytic streptococcus of Horder, *Streptococcus tenuens* of Hastings and the streptopneumococcus of Rosenow. Recently Libman has called it *Streptococcus anhaemolyticus*.

Not only is it impossible at the present time to arrive at a satisfactory classification of the various forms of streptococci, but their differentiation from the pneumococcus is even more difficult. Rosenow has advanced experimental proof of the transmutability of the two organisms. There is a great similarity between the *Streptococcus viridans* and the *Micrococcus rheumaticus*. Rosenow maintains that a differentiation is possible, but Major considers the two organisms as one and the same.

Regardless of the precise relationship, the *Streptococcus viridans* possesses certain peculiarities which are most important from a clinical consideration. Schottmüller in his original communication called attention to the fact that the organism grows very slowly. This has been confirmed by all subsequent observers and emphasized especially by Libman and Celler. The colonies rarely appear before thirty-six to forty-eight hours, usually later, and the plates should never be discarded as negative before the tenth or fourteenth day. On blood agar the colonies are very small, almost pin point, and appear slightly gray or distinctly green. The organisms have no capsule, are gram-positive, occur singly or in pairs and occasionally in short chains, which is the usual form when grown in 1 per cent peptone bouillon media. The organism is small, measuring 0.6 to 1 micron and grows best at a temperature of 37° C. Experimentally the virulence is very low, although it is resistant to phagocytosis and apparently develops a resistance to the antibodies.

The organisms are found imbedded in the vegetations and exist in the circulating blood. The number of organisms in the peripheral circulation may vary from a few to an almost uncountable number in each cubic centimeter of blood. The number bears no definite relation to the severity of the disease. Even in severe, terminal forms the blood may become bacteria-free and the patient fever-free. The first blood culture

is not always positive and in some cases several repeats may be required. As stated in the acute infective form, on more than a few occasions the catheterized urine has given a positive culture, with or without a positive blood.

The slowness with which the organism grows, its resistance to phagocytosis and the antibodies may help to explain its protracted clinical course and lack of response to therapeutic efforts.

PREDISPOSING CAUSES.—Associated or previous diseases are most important when considered from the standpoint of portal of infection or the endocardial changes produced, resulting in a tendency to reinfection.

The determination of the portal of entry may be, and usually is, impossible on account of the lack of clinical evidence or because all local symptoms and signs may long since have disappeared. Then again, the primary focus may be slight, perhaps inaccessible, or it is possible that the organisms gained an entrance without producing any local pathology.

According to Venning, it is possible in only 27 per cent of the autopsies in acute infective endocarditis to determine the primary focus. Great as the difficulty may be at autopsy, it becomes much greater clinically.

To attempt an enumeration of the various diseases considered as etiologically responsible would be a useless task, for many of them could by no means be held accountable.

A review of the literature gives one the impression of the importance of certain diseases, among which may be mentioned sinusitis, otitis media, rhinitis, infected tonsils, especially infected teeth and pyorrhea. Schottmüller isolated the *Streptococcus viridans* from a conjunctivitis, rhinitis, bronchitis, pulmonary abscess, appendicitis and enteritis. The last disease he considered as important, while Babcock emphasized appendicitis and cholecystitis.

In four recent cases in which the *Streptococcus viridans* was recovered in the blood, the endocarditis followed the extraction of a single abscessed tooth in three cases and, in the fourth, the removal of more than one.

Many recorded observations reiterate the frequency and importance of the presence of *Streptococcus viridans* in pyorrhea associated with endocarditis and arthritis.

Intimately associated with the problem of the portal of entry is the question of the various factors which influence the localization of the bacteria, with an apparent predilection for the endocardium.

All observers agree on the frequency and importance of a previous rheumatic infection, with a varying percentage as to the actual occurrence.

Horder (1920) reported a previous rheumatism in 50 per cent; Libman and Celler (1910) believe there is practically always a history of rheumatism, while Debré (1919) claims there is always a rheumatic history.

Admitting, as one must, the high percentage of a rheumatic infection in a subacute endocarditis, the next problem is the frequency of a rheumatic endocarditis as a predisposing cause. There is hardly sufficient available material to make a definite and positive statement, but it is

safe to assume that the percentage is fairly high in which the subacute endocarditis is engrafted on an old rheumatic endocarditis.

One of the most fascinating speculations in the discussion of subacute endocarditis is the consideration of the probable explanation of the intimate association of this disease with rheumatic infections and rheumatic endocarditis. The bacteriologic hypothesis will be considered first. Because of the existing uncertainty of the specific cause of rheumatism and the claim of some good authorities that the two organisms *Micrococcus rheumaticus* and *Streptococcus viridans* are one and the same, the theory may be advanced that the two diseases are only clinical variations of the same infection. Admitting this possibility, the theory of latency will assume importance and constitute a reasonable explanation. There is analogous proof of such a possibility in other infections, as in tuberculosis, syphilis and ordinary pyogenic infections, and perhaps there is no serious objection or inconsistency here, except that it is difficult to understand, if the two infections are the same, why the rheumatic endocarditis goes on to a recovery and the subacute to a fatal termination.

Perhaps the organism may possess the power of transmutation as described by Rosenow, which might easily account for any variation in the type of the organism as well as the differences in clinical manifestation.

The mechanical hypothesis is concerned with the local anatomic changes which favor reinfection, rather than the influence of the previous rheumatism. Schottmüller expresses the opinion that the valvular changes produced favor localization of the reinfecting organisms, but he fails to state in what manner.

Basically all of the mechanical theories have as their chief consideration the question of the decrease or increase of the vascularity of the valvular substance. The healed or healing rheumatic endocarditis is characterized by a process of organization of the vegetations with a gradually developing fibrosis of the leaflets. Pathologists have practically agreed that in a healed endocarditis the vascularity is decreased. Coombs, however, from his observations has arrived at an opposite conclusion—that the leaflets are more vascular.

Another hypothesis has to do with possible changes in the mechanism of immunity. Steinert believes that the reinfection may be due to an allergic reaction, which possibility presupposes a previous infection with the streptococcus. Rosenow, in his experimental work, has determined that the serum from the animals that have recovered from the infection with his modified pneumococcus has very little lytic or destructive power over the organism.

Perhaps this observation is to be explained on the assumption of acquired resistance of the infecting organism, as was previously mentioned. The further possibility is suggested by Coombs that the rheumatic infection lowers the immunity to infection with the *Streptococcus viridans*.

Local tissue immunity has been referred to as a possible factor, and, while admitting some influence, the preponderance of anatomic and ex-

perimental evidence is in favor of the greater importance of the general immunity, combined with local mechanical factors.

Pathology.—The description of the anatomic lesions includes not only the cardiac pathology but also the secondary extracardiac changes, both of which present distinguishing characteristics.

The lesions in the heart, as might be expected, are chiefly limited to the endocardium, involving particularly the left side of the heart, to which attention was directed in the discussion of the etiology. But there is a striking predilection for the mural portions of the endocardium, the intima of the pulmonary and aortic vessels, as well as the papillary muscles and chordae tendineae. This peculiarity is not pathognomonic of subacute bacterial endocarditis, but the frequency of the location and the extent of involvement are so pronounced as at once to constitute a feature highly suggestive of this type of the disease.

In contrast to the pronounced tendency for widespread involvement of the endocardium and intima of the vessels is the lack of extension and changes in the myocardium. This peculiarity is of clinical value and constitutes the anatomic basis for the lack of symptoms and signs of disturbed or broken compensation, at least in the earlier stages, in this form of endocarditis. Coronary complications, as thrombosis and emboli, while occasionally encountered, are characterized by their absence.

Another outstanding feature is the anatomic evidence of the previous rheumatic infection of the endocardium and myocardium, which constitutes such an influential predisposing factor in the reinfection of the heart, as well as determines the location of the infection. The valvular involvement, as regards the order of frequency, corresponds precisely with the previous rheumatic endocarditis.

Even the endocardial lesions present features more or less characteristic of this form of endocarditis. The valvular lesions in most cases are definitely proliferative, not destructive, resulting in small individual vegetations or large thrombotic masses. Occasionally there is a tendency to ulceration and destruction with loss of valvular substance, a perforation of a leaflet or production of a valvular aneurysm. Harbitz and Libman have emphasized in many instances the marked tendency to healing, as evidenced by the fibrosis and actual calcification. In addition to the anatomic changes, it is usually possible to isolate the causative organism, the *Streptococcus viridans*, from the vegetations.

The extracardiac lesions may be numerous and varied, some due to the systemic infection, others as the result of the accompanying toxemia, while the more important changes depend upon the occurrence of emboli and infarctions.

The systemic infection may occur as the blood invasion of some local focal infection of which the endocarditis is only a part, or it may be secondary to the infective process in the heart. While a primary or a secondary sepsis is frequent, local infections are infrequent. Pneumonia, particularly the bronchopneumonic type, abscess of the lung, liver or subcutaneous tissues, arthritis and other lesions may occur, but in most instances are due to a secondary pyogenic infection.

In one instance the clinical findings were those of a bronchopneumonia, while the anatomic changes were due to an infective periarteritis nodosa.

Meningitis, or more frequently an encephalitis, is a local lesion of the systemic infection. Mycotic embolic aneurysms are fairly frequent, especially of the cerebral and meningeal arteries, due to a combination of the infection and toxemia.

The toxemia, usually of low grade, produces the familiar cloudy swelling and parenchymatous changes as observed in any acute infection. Perhaps these changes are due to the chronicity rather than the acuteness of the toxemia.

The embolic lesions are comparatively much more frequent and important, producing anatomic changes some of which are quite characteristic and of the greatest importance clinically.

The vegetative or thrombotic emboli are responsible for the gross infarcts of the spleen, kidney, brain, mesentery and peripheral vessels. In a recent observation there was a simultaneous infarction of the right brachial and right popliteal arteries; while in the second instance embolization occurred in the spleen, right kidney and brain.

The bacterial or small thrombotic emboli produce the suggestive cutaneous and mucous membrane petechiae and hemorrhages, as well as the painful nodules of the peripheral phalanges of the fingers.

The renal changes are quite characteristic and practically pathognomonic of subacute bacterial endocarditis. The lesions were first described by Löhlein in 1910 and later confirmed by Baehr, Gaskell, Libman and others.

Macroscopically there is only a slight enlargement, the surface is smooth but covered with small punctate hemorrhages, to which appearance Gaskell has applied the term "fleabitten kidneys."

The histologic description of the lesions by Löhlein is that of an embolic nephritis due to bacterial embolization of the glomerular capillaries with the *Streptococcus viridans*. The extent of the lesion as well as the histologic changes varies with the stage of the disease. Baehr emphasizes certain peculiarities, "as the involvement of one or more loops of a variable number of glomeruli; the absence of any visible disease in the un-involved glomeruli and in the un-involved portions of affected glomeruli and the association in most of the bacterial cases of all stages of the glomerular process, often seen in a single microscopic section."

Due to the limited patchy involvement of the lesion, with much of the renal tissue remaining practically normal, there is little or no disturbance of the kidney function. In some of the more protracted cases the changes are those of an acute diffuse glomerulonephritis or a secondary contracted kidney, with resulting functional disturbance.

Symptomatology.—To give a typical, comprehensive clinical description is impossible on account of the protean type of onset and the varied group of symptoms. In most instances the symptoms and signs can be separated into two groups; those which appear early, suggestive

of an infective process, and those appearing later, the result of emboli, with infarctions, which present clinical evidence not only suggestive of endocarditis but lending a special character to the disease.

The symptoms of the earlier period are often very vague and indifferent. Perhaps the only complaint is a general malaise, fatiguability, poor appetite, loss in weight and insomnia. Chilly sensations, or definite chills, and fever appear, with sweats; a progressive anemia, and perhaps vague pains in some of the joints without local evidence of arthritis. Usually there are no symptoms or signs of disturbed cardiac compensation and so no suspicion is aroused of the seriousness of the ailment. After a varying period, which is not fixed, usually from a few days to a few weeks, the onset of the second period is ushered in by the sudden, oftentimes unexpected, appearance of external or internal emboli. The patient may complain of sudden, severe abdominal pain, either diffuse or in the upper left quadrant; perhaps the pain is localized in the lumbar region with a hematuria; an aphasia or hemiplegia may occur. Sometimes there is evidence of a blocking of one of the peripheral vessels and resulting gangrene. Concomitant with the embolic phenomenon, the weakness and anemia become progressively worse, with the chills and fever more pronounced.

During the earlier period careful physical examination fails to reveal any noteworthy findings except the signs of an old previous valvular lesion. Repeated examination may fail to detect any appreciable change in the type or character of the murmur—these negative findings allaying, at least momentarily, the fear of a reinfection.

The progress of the disease is confirmed by the appearance of petechiae on the skin or mucous membrane; perhaps emboli with infarction and with changing cardiac signs, which may finally become associated with evidence of disturbed myocardial function and decompensation.

The many and varied clinical symptoms and signs can advantageously be considered more in detail under separate headings.

ONSET.—The greater number of cases present a most insidious onset, as might be suspected from a consideration of the nature of the causative organism and the local pathology. In a smaller number the onset and course are comparatively acute, but it should be remembered that this impression is based on a clinical, symptomatic history and the exact time of onset may be quite indefinite. The one symptom preëminent is weakness, expressed in various terms as malaise, debility, asthenia, exhaustion and easily fatigued. Slight fever and perhaps chilly sensations come next in order of frequency, with cardiac symptoms and slight arthralgia.

When the onset is more acute and the symptoms more pronounced, it may simulate a low-grade infection or malaria; a subacute arthritis or sometimes an acute infection suggestive of a sepsis or puerperal fever.

THE FEVER, CHILLS AND SWEATS.—The combination of fever, weakness and loss of weight is fairly frequent, but the one symptom alone that causes anxiety is the abnormal temperature. As a rule, it is a

low-grade type of fever, perhaps subnormal in the morning and slightly elevated in the afternoon. The fluctuation-range from the low to the high point rarely exceeds more than three degrees.

Compared with the temperature curve in the acute bacterial form, it is much lower, more uniform, lacking the great fluctuations and irregularities. Chilly sensations or typical chills may precede the onset of the fever, to be followed by sweats, suggesting a possible malaria. Occasionally drenching, exhausting sweats are present, without chills or fever, occurring during the day or night, especially when the patient is sleeping, simulating the night sweats of pulmonary tuberculosis. The duration of the fever is variable, sometimes continuing throughout the entire course of the disease, sometimes of a recurrent type or with periods of apyrexia, which is more frequently observed in the protracted cases.

CUTANEOUS AND MUCOUS MEMBRANE MANIFESTATIONS.—Some of the skin or mucous membrane signs are most valuable and highly diagnostic. The most frequent lesion, and the one especially sought for in suspected cases, is the petechiae, which usually appear sooner or later in practically every case. They consist of small hemorrhages, either intracutaneous or into the submucous membrane, apparently due to bacterial emboli or small particles of the vegetations, as they often occur in crops, and frequently accompany the occurrence of a blocking of one of the larger vessels. The typical lesion is small, usually 1 to 1.5 mm. in diameter, the cutaneous lesions presenting at first a bluish color, later pinkish, not tender and not disappearing on pressure. Occasionally the lesions present an anemic or yellowish center, but practically never go on to suppuration or gangrene. Numerically there may be but one or two, of questionable character; more frequently the number is unlimited and the distribution universal. The site of election is the palpebral or bulbar conjunctiva; the mucous membrane of the mouth, especially the sublingual, labial, buccal or palatal portions; the cutaneous surface of the anterior portions of the neck and the axillary areas. A most diligent and thorough search, perhaps repeated many times, will be required to establish their presence or absence. They should not be confused with the small, bright red, slightly elevated telangiectases which are congenital or acquired and disappear on pressure.

When the lesions are numerous they may appear over the entire surface of the body.

Instead of the lesions remaining small, of the petechial type, they may be larger and become purpuric or even presenting the character of suggillations.

When the embolic process involves the fingers and toes, the lesions assume a special form and constitute a most important diagnostic significance. Their occurrence had been previously described, but Osler was the first to emphasize their clinical significance, and consequently they have been called Osler's sign. The lesion consists of a small, red, very painful or tender area, 0.5 to 1 cm. in diameter, usually slightly elevated and occurring on the pads or borders of the terminal phalanges of the fingers and toes. Similar to the petechiae, they appear in crops, usually single

but may be multiple. They were described by Osler as ephemeral, painful, nodular erythema; by the French as "faux panaris" and "signe des doigts." Janeway has described identical lesions, probably slightly larger, occurring in the palms of the hands and soles of the feet. The subungual hemorrhages were described by Horder, Lereboullet and Mouzon.

Some of the less frequent and important skin lesions consist of general erythema, erythema nodosum or multiforme.

CARDIAC MANIFESTATIONS.—It must be remembered that a preëxisting rheumatic endocarditis is the rule, which may be responsible for any disturbance of compensation and heart symptoms independent of the reinfection. How much is due to one or the other is no easy determination. The reinfection may aggravate the symptoms and signs, but oftentimes there is no obvious increase in the clinical evidence. One of the most frequent and suggestive symptoms is palpitation and cardiac distress, especially on physical exertion and excitement. Dyspnea, either constant or paroxysmal, is a fairly constant complaint. Cardiac pain, mild and indefinite, is by no means infrequent, while the severe anginoid type is encountered when there is coronary or aortic pathology.

The cardiac findings will depend on several factors. It may happen that the previous endocardial changes are so slight as not to produce symptoms or signs and the reinfection so located that it is unassociated with even a cardiac murmur.

In a small percentage the infection is located on the cardiac wall or septum of the heart, incapable of producing any functional disturbances and unassociated with a murmur throughout the entire clinical course. The same thing may take place without previous cardiac pathology. Usually the physical signs are those of the previous valvular lesion, which may remain unchanged or become modified, depending on the local pathology.

The previous rheumatic infection manifests a predilection for involvement of the mitral leaflets; then the aortic, as next in order of frequency; then aortic and mitral combined, followed by other less frequent forms, which is the identical order of frequency for the subacute endocarditis.

The occurrence of a subacute endocarditis is usually announced not only by symptoms but by an increase in the degree of the physical signs. Occasionally there is suddenly developed a low, musical murmur due to a perforation of one of the leaflets or rupture of a papillary muscle.

The radial pulse may reflect the type of valvular lesion present, as the aortic or mitral pulse, or perhaps present some variation in the rhythm. The normal rate is not uncommon, especially in the beginning, increasing as the disease progresses and frequently with extraventricular systoles, an auricular fibrillation or flutter. Clubbing of the fingers and toes is a fairly common finding, associated with the previous valvular lesion or perhaps due to the reinfection.

THE BLOOD.—One of the striking features of subacute endocarditis is the altered general appearance of the patient. One of the most fre-

quent changes consists of a high-grade anemia, perhaps with a subicteric or icteric tint. With or without the anemia, pigmentation of the skin sometimes occurs, perhaps limited about the face, simulating the chloasma areas of pregnancy, or the distribution is more diffuse, presenting a yellowish-brown color described by Libman as "café au lait."

The blood examination reveals variable findings but, generally speaking, the changes are those of a mild to a severe type of secondary anemia. The red cells may be decreased to 3,000,000 or 2,000,000 with a corresponding reduction of the hemoglobin to 70 or 50 per cent. The numerical determination of the leukocytes is of some importance, more so than the variation in the type of the cells. In the beginning there is a moderate-grade leukocytosis in a limited group, while in the greater number there is a definite leukopenia, progressive in nature, corresponding with the progress of the disease. This leukopenia is so constant and pronounced in a subacute endocarditis that its presence with a heart lesion at once suggests the existence of a *Streptococcus viridans*. The differential count is usually that of a secondary anemia and fails to present any distinguishing characteristics. It sometimes happens that the blood changes are so extreme that the condition has been described as the anemic type, or when the anemia is associated with an enlarged spleen, as the splenomegalic type. The enlarged spleen, the blood changes, weakness and general features simulate a splenic anemia. Blood cultures, with positive findings, constitute one of the most important confirmatory diagnostic aids. As stated previously, when considering the bacteriology of the disease, the organism is a slow-growing one, requiring several days, oftentimes ten to fourteen days. Repeated attempts may be required before a positive growth is obtained.

General adenopathy is an infrequent finding, although a septic, systemic infection is quite the rule. In a recent observation the autopsy findings revealed a subacute endocarditis, associated with a cervical adenopathy due to carcinomatous metastasis.

VASCULAR LESIONS.—Due to the general septic infection, there occasionally occurs a local infection of the arteries, a periarteritis nodosa. The usual form of involvement is due to embolic blocking of a peripheral vessel with gangrene, or the visceral organs become involved, producing symptoms and signs depending upon the location of the embolus.

One of the cardinal findings, in the clinical diagnosis of the disease, is the enlarged spleen, as determined by palpation or percussion. Some increase in size may be due to the infection and toxemia; usually the enlargement is due to embolization, single or multiple, which is usually announced by pain in the splenic region, with tenderness, increase in size and frequently a palpatory or auscultatory friction rub, due to the perisplenitis.

Ocular manifestations are comparatively frequent and important. Sudden blindness, due to embolism of the central artery, occurs in about 2 per cent and may be bilateral. Small retinal hemorrhages are even more common, occurring in about 8 per cent. Neuroretinitis, optic

neuritis or atrophy is occasionally found, while a suppurative panophthalmitis is rare. The eyes, including the fundi, should be examined carefully and repeatedly for any possible pathology.

Coronary occlusion, embolic or due to thrombosis, as well as embolic aneurysms, has also been described.

GENITO-URINARY MANIFESTATIONS.—Approximately one-third of the cases present evidence of renal infarction, either unilateral or bilateral, single or multiple. They can occur without pain or discomfort, but usually there is backache or real pain with hematuria, and sometimes ureteral colic due to the passage of a blood clot. Urinalysis reveals the presence of blood, pus cells and sometimes casts.

Renal pathology, aside from the gross emboli, is frequent and the changes are of a special type, associated with the endocarditis and due to the systemic infection. Urinalysis reveals the findings of a nephritis, but the symptoms and corresponding physical signs, as well as the blood chemistry changes, are wanting. The typical clinical findings of a renal edema, hypertension, secondary cardiac hypertrophy and protein retention in the blood are rare and occur only in the protracted cases.

In female cases amenorrhea or metrorrhagia may occur, due to the secondary anemia.

THE CEREBROSPINAL MANIFESTATIONS.—The kind and degree of the symptoms vary from a slight headache to a complete terminal coma. During the onset of the disease unilateral or diffuse headache, probably toxic in origin, is frequent. Later the severe type or actual pains may be due to emboli, meningitis or some other form of organic pathology.

Cerebral emboli, with aphasia, hemiplegia and other disturbances, have been reported in about 20 per cent of the cases.

Autopsy findings reveal the frequent presence of emboli, a cerebro-malacia and abscesses, but equally as often the anatomic changes are those of an encephalitis or meningo-encephalitis. The clinical symptoms of delirium, insomnia, melancholia or some type of psychosis, a diplopia, stupor and coma, even the aphasia and partial hemiplegias, may be due to an encephalitis or meningo-encephalitis.

In a few instances the *Streptococcus viridans* has been cultured from the spinal fluid.

THE GASTRO-INTESTINAL AND ABDOMINAL MANIFESTATIONS.—Excluding the embolic cases, the gastro-intestinal symptoms are not frequent, except in a few during the terminal stage.

Perhaps the one most important and not infrequent occurrence is a mesenteric embolism, producing an infarct and intestinal gangrene. There is usually severe abdominal pain, although occasionally it is absent, with or without nausea, vomiting, diarrhea and bowel hemorrhage.

If not at once fatal, a complicating, secondary suppurative peritonitis usually follows in a few hours.

Diarrhea, or alternating looseness with constipation, is sometimes due to intestinal emboli or bowel infection.

Loss of appetite, a secondary anemia, with an icteric tint, and a marked emaciation may occur and such patients are referred to as the cachectic type.

The Clinical Course, Duration and Mode of Termination.—The course of the disease is characterized by variability, with an irregularity, at times apparently improved, only to be followed by a relapse and general downward tendency.

The duration is also very uncertain, depending on the virulence of the infection, the extent of the pathologic involvement, the local and systemic immunity, as well as the possible complications. The greater number terminate in six weeks to two months, a few with an acute course may last only a few weeks, while the low-grade, protracted cases may go on for a period of two years or longer.

The mode of death is often a cardiac one, frequently with embolism or some complicating cardiac pathology. Other complications, as a pneumonia, meningitis or associated infection, are fairly frequent.

Diagnosis.—The insidious onset, with the varied symptoms and physical findings, renders the diagnosis anything but easy.

However, the combination of certain symptoms and signs may be suggestive and finally lead to a correct diagnosis.

There may be a pyrexia of unknown origin, the history of a previous heart lesion, recent exacerbation of cardiac symptoms, a palpable spleen and a low leukocyte count, all of which are consistent with an infective endocarditis. The appearance of petechiae, of emboli or Osler's nodules, with a positive blood or urine culture, practically establishes a diagnosis. It is well to reiterate that several blood cultures may be required before a positive one is obtained. Occasionally all attempts may be negative during the bacteria-free stage of the disease.

The disease has been subdivided into certain types, on account of some particular dominating feature of peculiarity. The following forms may be enumerated:

1. Septic or pyemic, with chills and fever.
2. Pseudomalarial, with regular recurrent chills and fever.
3. Pseudotuberculous or phthisic, with sweats and fever.
4. Anemic, simulating the primary or secondary.
5. Splenomegalic, with enlarged spleen and anemia, simulating some form of splenic anemia.
6. Apyretic, where the fever disappears and the blood usually becomes bacteria-free.
7. Cerebrospinal, either cerebral or cerebrospinal meningitis.
8. Psychotic or encephalitic.
9. Rheumatic, with arthralgia or arthritis.
10. "Mute form," where there is no murmur and perhaps no cardiac signs.
11. Renal, with urinary findings of a nephritis or urinary infection.
12. Embolic, in which petechiae and infarctions predominate.

DIFFERENTIAL DIAGNOSIS.—The differential diagnosis is concerned with the various diseases which the symptomatic manifestations simulate, some of which are evident in the enumerated list of clinical forms. When the pyrexia is the chief symptom any febrile disease is a possibility. Perhaps a typhoid fever, Malta fever, a malaria, a tuberculosis or some focal infection is suspected, especially as there is a fever, with a palpable spleen and a low white count—a possible symptom-complex common to all the mentioned diseases. Blood examination with cultures and agglutination tests will usually suffice in malaria, typhoid and Malta fever, even before the appearance of petechiae or emboli. Careful clinical and roentgen-ray examination, as well as repeated sputum examinations, will be of service in suspected pulmonary tuberculosis. Focal or systemic infections may be most confusing until the manifestations have so developed as to make the determination possible. A thyrotoxicosis, with a tachycardia and palpation, a loss in weight, sweating and slight fever, is occasionally diagnosed as endocarditis. The confusion can occur only in the earlier stages of either disease when the distinguishing features are wanting.

Urinary infections, a cystopyelitis, secondary to the infective process in the kidneys and a part of the endocarditis, or the hematuria of a renal infarction, have been particularly confusing and necessitate not only careful cystoscopic study but also cardiac examination, including blood cultures.

Having established the clinical diagnosis of an acute endocarditis, it becomes necessary to differentiate between an acute infective endocarditis and a subacute bacterial form. Some of the factors that may be of assistance are the following:

1. Previous history of infection, as pneumonia, sepsis, gonorrhea. Focal pyogenic infection usually precedes the acute infective form, while in the subacute bacterial there is no such history and only careful examination may reveal a possible focus of infection.

2. A sudden abrupt onset is more common in the acute infection; a slow insidious onset is typical of the subacute.

3. Chills, with an irregular septic pyrexia of considerable degree, occur with the acute infective; the subacute is accompanied by a lower and more constant type of fever.

4. Petechiae and emboli are common to both forms but far more frequent in the subacute bacterial.

5. Osler's nodules, Janeway's signs and the subungual hemorrhages are practically pathognomonic of the subacute bacterial form.

6. The duration of the acute infective is comparatively short; the subacute bacterial is characterized by a prolonged course.

7. In the acute infective the local pathology is more destructive, leading to a perforation of a valve, the septum of the heart or the cardiac wall; occasionally the rupture of a papillary muscle or more frequently a complicating acute myocarditis. The virulence of the infection in the subacute bacterial is relatively low and the local pathology correspondingly limited.

8. A moderate or relatively high leukocytosis is the rule in the acute infective; a relatively low leukocytosis or more frequently a leukopenia is quite constant and suggestive of the subacute bacterial.

9. The blood cultures are important and, according to the definition, the infective organism in the subacute bacterial form is limited to the specific bacteria, the *Streptococcus viridans*. Other varieties of bacteria may be isolated in the acute infective.

10. There is a difference in the final outcome; the subacute bacterial practically is always fatal, while the acute infective may go on to a recovery.

Treatment.—There is no specific or even recognized treatment for acute endocarditis. As far as can be determined, all therapeutic efforts and attempts of various kinds are simply useless and futile. These comments apply especially to the subacute bacterial form but with practically equal force in the acute infective type, both of which are being considered collectively.

Some prophylactic form of therapy would be the one of choice, preventing not only the reinfection of the heart, but also the primary rheumatic endocarditis, which plays so important a part as a predisposing factor. As to the prevention of a rheumatic endocarditis, we have already learned our therapeutic limitations, when the subject was previously considered.

The proper, accepted **treatment of the previous or accompanying disease** is perhaps as important as any measure, particularly when combined with **rest in bed**. Admitting our inability to prevent the primary rheumatic endocarditis, as well as the reinfection, we can now turn our attention to a discussion of the various recognized efforts and attempts to combat the reinfection once it has occurred.

As the disease acute endocarditis is due to some form of bacterial infection, it might be natural and logical to anticipate beneficial results from the therapeutic use of a vaccine, either autogenous or stock. With the advent of vaccine therapy in the various infective diseases, there were aroused great hopes and expectations, but at present there is a general opinion that the **vaccine therapy has been tried and found wanting**. This is true of the autogenous or stock vaccine, whether given intravenously or subcutaneously or by mouth. **Serotherapy**, employing either stock antistreptococcus sera or one prepared by inoculating animals with the specific isolated organism, has produced no better results than the vaccine therapy.

In view of the failure of the vaccine and serotherapy, it is rather surprising that a combination of the two has been suggested and employed. Hemsted reports one case with a recovery that was treated with autogenous vaccines, 2,000,000 to 15,000,000 for four months; this was followed by five doses of serum, which in turn was followed by the vaccine.

Blood transfusions, using the whole or citrated blood, have been employed rather extensively, with some possible benefit in the anemic

or hemorrhagic type of cases, but without any evident effect on the infection, as blood is not bactericidal. The same unhappy results have followed blood transfusions in vaccinated donors, using the autogenous vaccine made from the isolated organism in the blood cultures. Lamb and Blumer each report one case, with failure which is in accord with the result in four personal observations.

Autoserotherapy, suggested by Abrahams, in which 20 cc. of the patient's own serum are injected intravenously or subcutaneously, has produced no benefit in proved cases.

Subcutaneous injections of leukocytic extract, with the object of producing a leukocytosis, can be mentioned as one of the discarded methods.

Chemotherapy claims many advocates and a considerable list of various substances for oral, subcutaneous or intravenous administration. Quinine, hexamethylenamine and salicylates by mouth have resulted only in failure. Leschke has reported the same result in the use of large doses of optochin and iso-amylhydrocuprein.

Various preparations of silver, arsenic, antiseptics and the aniline dyes have all in turn had their day, only to be replaced by others of temporary and fleeting favor. Silver in the form of Credé's ointment was used externally, while other preparations, as collargol especially, were given intravenously, but without effect on the local infection or in producing a leukocytosis. As to the use of the **arsenicals**, there is a wide division of opinion; Debré reports no benefit and Lorey observed one apparent recovery with salvarsan. It is safe to state, however, that practically all observers agree with Debré, regardless of whether salvarsan, arsphenamine or neoarsphenamine is used. Frank Billings and others have expressed a preference for **sodium cacodylate**, which may be given subcutaneously or preferably intravenously; when given subcutaneously, 10 to 15 gr. (0.65 to 1 gm.) may be employed every second or third day for a month or six weeks, when it is discontinued, to be resumed later as may be determined. The same amount can be given intravenously but for a shorter period of time. The writer favors 3 to 5 gr. (0.195 to 0.3 gm.) given daily over a period of six weeks or two months, depending upon circumstances.

Other preparations given intravenously including solutions of mercurochrome, acriflavine and some of the aniline dyes, particularly gentian violet, were all one-time favorites, but at present are no longer in evidence. Mercurochrome, the most promising member of this group, produced no evident benefit and has the disadvantage of inducing chills and fever. In one instance at least, at the height of a rigor, an embolus and cerebral infarct were produced. When the heart becomes decompensated, **the usual recognized therapeutic measures** may be employed but with less probability of benefit as compared with similar indications in the chronic myocardial or valvular lesions.

Careful consideration of the treatment of acute endocarditis, as given, can only lead to the conclusion that it is most unsatisfactory,

practically useless and futile. An occasional recovery may apparently take place, not due to but in spite of our efforts.

Prognosis.—According to unanimous opinion the prognosis is bad. From start to finish there is only an unfavorable outlook although at times the periods of remission may be sufficient to sustain a growing hope and expectation, only to be dissipated by the subsequent unfavorable course. A review and study of the recorded cases reveals that the disease may end in apparent recovery, but this is rare and the exception. Perhaps a liberal estimate is 1 per cent; certainly not in excess of 2 per cent. In estimating the prognosis it is necessary to keep in mind the difficulty of the clinical diagnosis and only conclusively proved cases should be taken as a basis of percentage determination.

CHAPTER III

CHRONIC VALVULAR DISEASE OF THE HEART

By THOMAS F. KELLY, M.D., F.A.C.P.

- Introduction, p. 91.
- Aortic stenosis, p. 93:—Etiology, p. 93; Symptomatology, p. 93; Diagnosis, p. 96; Prognosis, p. 97; Pathology, p. 98.
- Aortic insufficiency (Aortic regurgitation), p. 97:—Etiology, p. 99; Symptomatology, p. 100; Diagnosis, p. 106; Treatment, p. 107; Prognosis, p. 109; Pathology, p. 111.
- Mitral regurgitation, p. 112:—Etiology, p. 112; Symptomatology, p. 113; Diagnosis, p. 120; Prognosis, p. 123; Pathology, p. 126.
- Mitral stenosis, p. 127:—Etiology, p. 127; Symptomatology, p. 128; Diagnosis, p. 134; Complications and sequelæ, p. 139; Prognosis, p. 141; Pathology, p. 144.
- Tricuspid regurgitation, p. 146:—Etiology, p. 146; Symptomatology, p. 147; Differential diagnosis, p. 148; Prognosis, p. 148; Pathology, p. 149.
- Tricuspid stenosis, p. 149:—Etiology, p. 149; Symptomatology, p. 149; Diagnosis, p. 149; Prognosis, p. 150; Pathology, p. 151.
- Pulmonary stenosis, p. 151:—Etiology, p. 151; Symptomatology, p. 151; Diagnosis, p. 151; Prognosis, p. 152; Pathology, p. 152.
- Pulmonary regurgitation, p. 152:—Etiology, p. 152; Symptomatology, p. 152; Differential diagnosis, p. 153; Prognosis, p. 153; Pathology, p. 154.
- General prognosis of chronic valvular disease, p. 154:—Cause of cardiac lesion, p. 156; Kind of person who has heart disease, p. 158; Conditions affecting the prognosis, p. 160.
- General treatment of valvular disease, p. 164:—Cases discovered by accident and presenting no symptoms, p. 164; Outline of treatment, p. 166—Cases presenting minor symptoms accompanying valvular disease, p. 166:—Special indications, p. 169; Outline of treatment, p. 171—Individual symptoms and their treatment, p. 172—Broken compensation:—Diet, p. 184; Hope, p. 185; Digitalis, p. 185; Other preparations of digitalis, p. 188; Substitutes for digitalis, p. 189; Indications for the use of digitalis, p. 190; Contra-indications to the use of digitalis, p. 190; Opium, p. 191; Other drugs of use in cardiac disease, p. 192; Therapeutic measures other than drugs, p. 195; Outline of treatment in decompensation, p. 200.

Introduction.—About 5 per cent. of all patients met with in general practice have chronic valvular disease of the heart. This percentage is much larger in hospital practice, wherein it reaches from 10 to 15 per cent., depending upon the nature of the service, *i.e.*, whether it is an ambulance service or a selective service. The results of many thousands of examinations of school children by the Health Department of New York show that more than 1 per cent. suffer from serious chronic valvu-

lar disease. During the last decade the attention of the profession has been directed more particularly toward the study of the muscles of the heart than of the valves. Any one who has seen, at autopsy, the hard and sclerotic valve, which is sometimes even calcareous throughout and which, however, must have functioned for years in that condition, cannot help being struck with the idea that it requires more than a damaged valve to produce a break in compensation. This added factor is the muscle of the heart, and upon it, more than upon the condition of the valve, depends the ultimate basis of the patient's outlook for life. The demonstration of Aschoff's bodies in the muscle of the heart in the course of rheumatic infection, proving that such bodies are the foundation of a later specific sclerosis in the muscle and that they are coincident with vegetative involvement of the edges of the valves, has gone far to confute the opinion that the infection involves the valves alone, and has indicated that it commonly involves the whole heart when any portion of it is involved. For that reason the importance of the physical signs of endocarditis is largely indirect. The signs of valvular disease prove that one part of the heart has certainly been damaged by some agent, and that it is almost certain that other portions of that organ are likewise involved. Unfortunately, in the vast majority of cases, we have no other physical means of estimating what the nature of the damage done has been, except by auscultation of the valve sounds. One must hasten to add that symptoms are of far more import from a diagnostic and prognostic standpoint than are any or all of the physical signs, and that when they are well marked, they are our best guide in arriving at any conclusion. However, unless there is something definitely diagnostic in these phenomena, in the absence of physical signs, one cannot, in the early stages of diseases, give a positive opinion as to their organic significance. For instance, dyspnea, the cardinal symptom of heart-failure, may be due to the diseases of the lungs, blood or mediastinum, and in the absence of some indication of a physical change in the heart there is no way of arriving at a conclusion. Irregularities of the heart-beat indicate that there may be some degeneration of the muscle. Irregularities which can be of diagnostic or prognostic import early in the course of the disease are comparatively uncommon in proportion to the total number of cases of cardiac involvement. The elucidation of the odd and unusual irregularities can only be accomplished by instrumental means in hospitals and institutions in which much time can be devoted to solving these problems. In any event the net result is almost always academic rather than practical. It is safe to say that, with the exception of auricular fibrillation, the number of such cases presenting nothing but the evidence of damage to a muscle, as revealed on a pulse-tracing or electrocardiogram, are negligible, as compared with the number of patients suffering from endocarditis and myocarditis.

The necessity for a study of the valve-sounds is especially evident in children, because here information as to the muscle condition is rarely obtainable through tracings. In more than 80 per cent. of the patients

presenting evidence of broken compensation some abnormality of the valve sounds will be found which can be described in an intelligible manner and which can be evaluated by the practitioner. For this reason study of the condition of the valves, as determined by the practitioner by ordinary physical means, is the best objective index which we have at the present time of the conditions existing in the heart.

It is frequently argued that the close differentiation between the various valve lesions has only an academic value, and that after all the absence of loss of compensation is the important feature. While this is true to a certain degree in well-marked and advanced cases, such as are commonly seen in hospital practice, there are essential differences in the symptomatology, and especially in the prognosis of early and moderately advanced cases, which render the close study of the individual valve symptoms a necessity.

AORTIC STENOSIS

Etiology.—Aortic stenosis as an uncomplicated lesion is very rare. In a large hospital service it occurs once or twice a year and is a curiosity. As a combined lesion, however, in association with aortic regurgitation, it is not so rare; yet here the associated lesion commonly masks the signs and symptoms of stenosis. It is present in about one-half of one per cent. of all cardiac valvular lesions. When found as an isolated lesion it is rarely due to rheumatic fever, but is commonly associated with arteriosclerosis. Most of the supposed aortic stenoses in which the diagnosis is made on the strength of the presence of an aortic systolic murmur before the patient is fifty years of age are due to changes in the blood, producing hemic murmurs, while most of those made in patients over fifty years of age are due to arteriosclerotic changes in the aorta. Aortic stenosis is far more common in men than in women, and is rarely apparent before middle life. It is due either to a previous attack of endocarditis or to a degenerative process. When it is due to endocarditis there is usually a concomitant involvement of the mitral valve.

Symptomatology.—These patients rarely complain of symptoms which are in any way characteristic of the disease. As in all basal affections of the heart, there is a sense of constriction or pain over the second right costal cartilage which is referred to the back. This is most common in the cases due to degenerative lesions. If the cause of the lesion is a former attack of endocarditis the symptoms do not appear for many years after the original disease. Of the minor symptoms, *dizziness* and *vertigo* are more commonly present than is the case in any other valve lesion. These are the symptoms which most frequently call attention to the lesion. Old people especially complain of these manifestations on lying down and getting up quickly. In the case of men they are most noticeable when the barber's chair in which they are lying is being raised or lowered. This is due to cerebral anemia. Occa-

sionally fainting attacks occur and are due to the same cause. In estimating the significance of these symptoms occurring in conjunction with a systolic aortic murmur, one must always keep in mind the fact that they may be due to other causes, such as cerebral arteriosclerosis associated with a roughened aorta. When there is any failure in compensation, however, the associated functional mitral insufficiency is responsible for the symptoms. This manifests itself commonly as shortness of breath on exertion. As the patient is usually well advanced in life by this time it acts as a red light of danger, warning him of the limitation of his activity, and thus prevents undue dilatation. For this reason careful living may prolong life for many years after the discovery of the lesion.

PHYSICAL SIGNS.—Observation.—Observation seldom reveals anything, because at the time of life at which the lesion becomes apparent, even if the heart does enlarge, the chest-wall is so rigid that it does not expand enough to render the enlargement noticeable.

Palpation.—A systolic thrill over the base in the second right intercostal space near the sternum is commonly present, although it is not pathognomonic, as it is often associated with other cardiac or vascular diseases. The apex-beat, when it can be felt at all, is seldom noticeable beyond the nipple line, and is usually in the sixth intercostal space. However, more often the apex-beat is *missing*, and this absence is a startling phenomenon. When it happens in any chest examination it calls for a careful scrutiny as to the cause.

(a) **Pulse.**—The pulse is slow, small, hard and regular. It is seldom more than 60 to the minute. It is frequently quite characteristic, and is often the sole deciding factor in determining the diagnosis. The wave is greatly prolonged and it seems to the examiner as though it would never drop. The artery is generally quite full between beats. This is due to the relatively small size of the aortic orifice, which permits only a small amount of blood to pass through at any one time, so that in order that the ventricle may empty itself a longer period of systole is necessary.

Percussion.—It is frequently difficult to map out the size of the enlarged heart by percussion because of the emphysema which so often accompanies this lesion in old people. This emphysema also accounts, at times, for the absence of the apex-beat.

Auscultation.—The systolic murmur so commonly heard at the base of the heart and transmitted up into the vessels of the neck is the least dependable, from a diagnostic standpoint, of any of the murmurs associated with valvular disease of the heart, because it is more often due to changes in the wall of the aorta than to changes in the valves themselves. It is heard with maximum intensity just outside of the right edge of the sternum in the second intercostal space. Occasionally, if one moves the stethoscope downward from the point of maximum intensity along the sternum, the murmur is lost over the body of the right ventricle. When the stethoscope is moved along to the apex the murmur may be heard here if hypertrophy is present. This is due to the transmission of the sound along the muscles of the left ventricle down to the apex where

they come close to the chest-wall. This is, however, a rather uncommon phenomenon. It has been asserted that this murmur at the apex disappears when pressure is exerted with the stethoscope. It must be differentiated from mitral regurgitation by other signs. When true aortic stenosis exists the murmur is not only transmitted up the aorta, but is usually heard on the right border of the sternum as far down as the fourth rib. The murmur is long drawn out and is of a hissing character. The first sound of the heart is usually absent at the base, the bruit taking its place. When the murmur is loud it may be heard at a greater distance from the chest-wall than any other murmur. The nature of the aortic second sound is of more value diagnostically than the presence of the murmur itself. It is a very faint sound (often absent altogether), and can scarcely be heard, due to the fact that the valves cannot close tightly together; consequently, an accompanying aortic regurgitation is most always present. If a good strong second aortic sound is present, the observer is justified in believing that the systolic murmur is due to changes in the aorta and not in the valves.

The first sound at the apex, when it can be heard, is dull and prolonged, and may be accompanied by the systolic murmur mentioned above, which has been transmitted down along the ventricle to the apex. When a true systolic murmur at the base is accompanied by the above-mentioned signs at the apex in a young person, the diagnosis of aortic stenosis is warranted. After middle life this rule does not always apply. In such a case the presence of an accentuated second aortic sound instead of a weak or missing second sound would indicate atheroma and dilatation of the aorta rather than aortic stenosis.

SPECIAL EXAMINATIONS.—Blood-pressure.—There are no characteristic changes unless there is associated arterial disease or aortic regurgitation, in which instances the pressure is usually higher than normal.

Sphygmograph.—In well-advanced cases the tracing is pathognomonic; it shows a pulse of small amplitude, the percussion wave is oblique, and the summit is gradually attained and continues much longer than normally. It is called the anacrotic pulse-tracing. A somewhat similar form, the pulsus bisferiens, is sometimes present, but it is not as characteristic as the anacrotic. When aortic regurgitation is also present this pulse-tracing is not so definite.

Electrocardiograph.—The R-wave of the electrocardiogram is directed downward in lead 3. This is not diagnostic of aortic stenosis, but shows the presence of a left ventricular hypertrophy, which is always present, and which, in conjunction with other signs, is helpful in arriving at the diagnosis.

X-ray Examination.—The orthodiagram shows enlargement of the heart-shadow to the left. The lower portion produces the appearance of a horizontal oval above which the shadows of the pulmonary artery and of the aorta are quite visible. The shadow in general resembles that present in aortic regurgitation, but is smaller than is usually the case in uncomplicated instances of the latter lesion.

Diagnosis.—Greater care must be exercised in the diagnosis of this than of any other valvular lesion. The region at the base of the heart has been well named the region of romance in diagnosis. The most common error is to diagnose a condition as aortic stenosis because of a roughening of the aorta which produces a basal systolic murmur transmitted up into the vessels of the neck. Such a murmur is a very common finding in patients over fifty years of age. The character of the murmur is the same as that of aortic stenosis. There is, however, an absence of the other signs associated with aortic stenosis, such as hypertrophy, feeble second aortic sound, and characteristic pulse. In the cases of sclerosis of the aorta associated with a systolic murmur, on the contrary, one finds that the aortic second sound is loud, clanging and accentuated, due to the increase of arterial tension associated with general arterial sclerosis. The feeble or absent second aortic sound of aortic stenosis is due to the stiffness of the aortic segments and their slow recoil which follows the relatively slow distention of the arteries. A history of rheumatic fever or of syphilis would indicate aortic stenosis rather than arteriosclerosis of the aorta as a cause. An acute *aortitis* may be confusing when seen for the first time. It produces a similar murmur; it is commonly associated with substernal oppression or a pain radiating out into the shoulder, and with dyspnea on slight exertion. There is a marked accentuation of the second aortic sound, and a more rapid pulse. Similarly, in rare instances, a dilatation of the aorta due to any cause may be accompanied by a basal systolic murmur. In such cases there is a dullness at the base, and a clanging accentuated second sound.

Hemic murmurs are frequently responsible for basal systolic bruits. These hemic murmurs accompany the first sound and do not take its place. They are often multiple and can generally be heard over the larger vessels throughout the body, if pressure is applied over them with a stethoscope. It is seldom that such a murmur is as loud as is that of aortic stenosis. A murmur of similar character to that of the hemic murmur is present in the asthenia of acute disease, and it is particularly common under such conditions in small children. More than 20 per cent. of small children with a continued temperature show some such systolic basal murmur. This disappears during convalescence. It is not far transmitted, nor are any other characteristics of aortic stenosis present. Its origin is similar to that of the hemic murmur, and it is of no evil consequence.

A *mediastinal tumor* may cause pressure on the aorta and thus be responsible for an aortic systolic bruit that is transmitted up the vessels of the neck. In such instances there is an enlarged area of dullness at the base; there is no alteration of the second sound, nor displacement at the apex.

Pulmonary stenosis produces intrinsically the same physical signs on palpation and auscultation as does aortic stenosis. It is a disease of youth and is almost always congenital or associated with some other lesion. It is not often a cause of difficulty in diagnosis. The chief point

in differentiation from the standpoint of physical signs is the fact that the murmur is not transmitted up the arteries of the neck. It can best be heard to the left of the sternum rather than to the right. The pulse is decidedly different, and there is hypertrophy of the right ventricle, whereas in aortic stenosis there is hypertrophy of the left.

When the aortic stenotic murmur is very loud and is heard quite distinctly at the apex it may be a question whether this is transmitted from the base or whether a secondary mitral regurgitation is present. If the latter is the case the condition is usually a relative mitral regurgitation, and other evidences of broken compensation will be present, especially the complaint of dyspnea on slight exertion. If a true organic lesion is also present in the mitral valve, a gradual diminution of the apical murmur will be noted on moving the stethoscope upward from the apex toward the base, and about the third interspace the basal systolic murmur will begin to appear.

The accentuated second pulmonic sound of mitral disease is of great diagnostic value in such instances and usually there are other evidences of mitral disease as well.

When the murmurs of aortic stenosis and aortic regurgitation are both heard the question often arises as to whether a true stenosis is present or whether the murmur is due to the thickened, roughened valve of aortic regurgitation. If the pulse is sudden or collapsing there is no room for doubt that the lesion is regurgitation, and this is by far the commonest condition. In the absence of such a pulse one is justified in feeling that stenosis is the predominating lesion. Finally, to recapitulate, there are four findings which are requisite as a basis for the diagnosis of aortic stenosis. Three of these should certainly be present: First, a systolic thrill at the base; second, a slow lazy pulse, and third, a systolic murmur best heard at the second right costal cartilage and transmitted up the vessels of the neck and usually down the right side of the sternum, and fourth, a faint or scarcely noticeable second aortic sound.

Prognosis.—In general the prognosis depends upon the cause. In a well-developed case in a young adult, where there is no question as to the diagnosis, the lesion is usually a progressive one, and death is at most only a matter of a year or two. The average duration of life in aortic stenosis, from the time of its recognition, has been placed at four years. According to Broadbent the average age of death in such patients is forty years. In the cases which develop late in life as the result of sclerosis (and these are the most common type) the outlook is very much better. The luetic cases, if recognized before the onset of symptoms, are curable. After the symptoms have appeared, little is to be hoped for in the way of permanent improvement. If there is a coincident involvement of the mitral orifice the prognosis is much worse. When the disease is combined with aortic regurgitation, as is so often the case, the course of the latter determines the prognosis. The immediate outlook depends (1) upon the degree of stricture, as determined by the

VOL. VI.—7.

character of the pulse, and (2) upon the condition of the muscle, as determined by the presence of symptoms, such as pain, dyspnea, etc. When the heart is not enlarged and the apex is in the right location, there is no cause for alarm. The same holds true if no subjective or objective symptoms are present after moderate exertion. In these favorable cases the pulse is slow and regular, and the pulse-wave is typical. The presence of auricular fibrillation in the sclerotic form is more serious than in other valvular lesions, inasmuch as it does not react to digitalis and the patient does not long survive its onset. Repeated attacks of fainting, dyspnea on exertion and marked dullness of intellect are strongly suggestive of approaching loss of compensation. These mental disturbances are quite common even a year before there is decided loss of compensation. The cases of aortic stenosis associated with anginal attacks, or with pain on exertion, are distinctly serious, no matter what the original cause of the lesion may be. It is true that some of these patients survive such attacks for a few years, but they are apt to die suddenly. In a fair percentage of cases, young patients suffering from aortic stenosis develop fatal pulmonary tuberculosis. In general, the subjects of aortic stenosis are always living up to the limit of their endurance, as it were, and have reserve of energy to draw on in an emergency, such as follows extra exertion or an infectious disease. When such an event occurs and compensation begins to fail, rest and medicines do not put the patient on his feet again, as is the case with other lesions, and the progress is steadily downward from the time of the appearance of the first definite symptom.

Pathology.—The lesion is either the result of a previous endocarditis or is due to sclerosis. In the endocarditic form there is a thickening of the valve edges, and organization of the vegetation which is present, and finally sclerosis. Later on in life infiltration with calcareous material takes place, and the orifice may be a rigid ring instead of a valve. In the arteriosclerotic form, which is by far the most common, and which is part of a general arteriosclerosis, the changes which take place in the valves are similar to those taking place in the inner coat of all the blood-vessels in that individual. Not infrequently on postmortem such valves feel hard and sclerosed, and yet there is no apparent stenosis. Hypertrophy of the left ventricle is marked, but is less evident than in regurgitation. At first concentric hypertrophy is present. Later dilatation appears. Because of the contraction of the orifice the ventricle is not able to expel all the blood which it contains during systole. After each succeeding diastole blood is left from the preceding contraction, thus causing a more strenuous systole than before. This accounts for the early hypertrophy. In addition the smaller size of the orifice causes systole to be greatly prolonged in its effort to expel as much blood as possible, and this accounts for the continued pulse-wave. When the muscle cannot overcome these factors dilatation of the left ventricle must result, and relative mitral regurgitation is the usual consequence.

AORTIC INSUFFICIENCY (AORTIC REGURGITATION)

Etiology.—Aortic insufficiency is the commonest lesion at the aortic orifice. It is present forty times as frequently as aortic stenosis, and it is much more common in males than in females. It is a disease of middle age. Osler has well said that the causes of this disease may be symbolically represented by Venus, Vulcan and Bacchus. According to statistics collected in many large cities, at least 75 per cent. of the cases are due to lues. This percentage does not hold true for all localities, but certainly more than one-half of all cases are luetic, and it is well to regard lues as the cause until otherwise proven. This is even more markedly true among negroes than among whites. The reason for this affinity of lues for the aortic orifice is not always clear, but inasmuch as in 50 per cent. of all cases of lues there is some involvement of the circulatory organs and as involvement of any structure in the body by lues is in direct proportion to the amount of stress or irritation to which it is subjected, this relative percentage of vascular disease occurring in the course of lues may be conveniently remembered by associating it with rheumatic fever which affects the adult heart also in 50 per cent. of the cases. The tissues of the aortic orifice are most commonly affected because they are constantly under strain and tension.

Visible evidences of this traumatic predilection of lues is found in the eruptions, which are most commonly visible in the skin at the hat-band, wristband and at the mucocutaneous openings. If cases of lues are auscultated during the first few months of the disease, particularly after severe exertion, it is surprising to find how many of them exhibit cardiac murmurs. Those who receive adequate treatment seldom present such murmurs during the active stage of the disease, and doubtless, with the newer methods of treatment and better general knowledge of the disease among the profession, aortic valve disease will be less common in the next cycle. Usually those who had not been adequately treated do not complain of symptoms until about fifteen years after the appearance of the initial lesion.

Hard work and *alcohol* are common causes of arteriosclerosis in middle-aged men, and as such they represent fully a third of the remaining cases of aortic regurgitation. This form of the disease usually progresses very slowly.

The remainder of the cases, with a few exceptions mentioned below, are due to *infection*. Of these infections rheumatic endocarditis is the most frequent. The rheumatic fever of childhood is the condition in which the aortic valves are usually affected. Such involvement is rare in the rheumatic fever of adult life. When rheumatic fever is a cause the mitral valves are also commonly involved. These double lesion cases are of special interest, inasmuch as later in life a malignant endocarditis following infection is much more likely to occur than in those

in which there is only a single lesion. Gonorrhea attacks the aortic in preference to the mitral valve, but it is a rare cause.

The few cases which are due to (1) traumatic rupture of the aortic cusps, (2) dilatation of an aneurysm of the ascending portion of the arch, and (3) congenital malformation, are sufficiently rare to be regarded as pathological curiosities.

Symptomatology.—It is not always possible to draw a sharp line separating the symptoms of the valvular lesions from one another, nor can a course be drawn which will fit all cases. However, the symptoms of aortic disease are more definite than those of other diseases; and even when other cardiac valve diseases are superimposed the aortic syndrome dominates the picture.

A patient suffering from aortic disease may, and usually does, live for many years, suffering from time to time from what he considers to be minor symptoms. These are so slight that he rarely consults a physician, and close questioning will nearly always show that such symptoms have been present for five or ten years before a really severe break in compensation occurs. The earliest symptoms are those of cerebral anemia. This is due to disturbances of a mechanical character because of the circulatory changes resulting from the valve defect itself, and also from the coincident arterial changes in the brain itself. The earliest of these are: Loss of memory, roaring and thumping in the ears, relieved slightly by inflation, spots before the eyes, disturbances in sleep, and nose-bleed. Insomnia usually occurs in spells, and distressing dreams are frequent. Vertigo and partial fainting spells occur when the patient suddenly stands up or lies down. From time to time headaches are of frequent occurrence; they are usually temporal, and occur especially after exertion. Fits of mental depression and exhilaration are the rule. These are all thought to be due to nervousness; in fact, in this disease, more than in any other form of heart lesion, there is a remarkable reaction to mental influences. The pulse-rate increases, and the caliber of the vessels often changes at the least news of a startling character. Digestive troubles occur, but they are not characteristic. The facial appearance is that of a grayish-white anemia. The florid type is very rare.

The symptoms which lead the patients to consult the physician are usually pain and dyspnea. The pain is variously described. In many cases there is only a sense of oppression or fullness over the precordium. In others a sense of constriction or of weight in the chest is noted. In most cases, however, the pain is sharp and sudden and follows exertion or after a heavy meal. Most commonly it radiates down the left arm, usually along the inner surface, first to the elbow and later down to the little finger. Occasionally it involves both arms. These pains occur, of course, in aortitis and in other myocardial diseases, but they are more often associated with aortic than with mitral disease. After the pain has passed off there is usually a sense of numbness or recollection of pain, noticeable for some hours. Once the symptoms of secondary mitral insufficiency appear pain is seldom an outstanding symptom.

The dyspnea is of gradual onset, except, occasionally, when it occurs following severe exertion. It represents a functional insufficiency of the mitral valve. After a longer or shorter period the attacks of shortness of breath wake the patient out of his sleep. At first he can usually fall asleep again. After a time restlessness supervenes after the attack, and sound sleep is impossible for the rest of the night. Later on, Cheyne-Stokes breathing is quite frequently present. When this is noted the outlook is ominous.

Attacks of acute suffocative pulmonary edema are more common than in any other form of valvular disease, and they are usually associated with sclerosis of the aorta. These attacks come on suddenly, last for half an hour or more, and then disappear. The patient looks frightfully ill, but death during the attack is exceptional. Coughing and lung involvement do not commonly appear until mitral insufficiency takes place. During each break in compensation a fever of from 37.77° to 38.33° C. (99.99° to 100.99° F.) may be present, due either to a complication or to a recurring endocarditis. The presence of stenosis with regurgitation augurs better than either condition alone, inasmuch as when failure in compensation occurs it is more gradual and resembles the failure in mitral disease rather than that of aortic disease. Whether this is due to a lessening of the reflux of blood or to the fact that the patient feels that he must live a quieter life is open to question. Certainly the prognosis is better in the case of patients who present a double aortic lesion with symptoms than in those suffering from aortic regurgitation alone and accompanied by the same group of symptoms. Once the presence of either well-marked, frequent attacks of stenocardia, or of dyspnea on slight exertion occurs, the prognosis grows steadily worse. Soon there is further dilatation of the ventricle and relative insufficiency of the mitral valve, and the symptoms of mitral disease are added to the clinical picture. From now on the symptoms are those of broken compensation in general. Fits of melancholy and depression are the rule at this stage.

Even early in the disease an anxious expression may frequently be noticed in patients suffering from heart disease, and is spoken of as the cardiac facies. There is usually an anxious, staring look in the eyes, and tenseness of the mouth, and in the aortic cases there is a distinct widening of the palpebral slits. This closely resembles the facies of exophthalmic goiter. Sooner or later most patients with cardiac involvement who are bed-ridden show some mental aberration. At first it is only momentary—a single bizarre or uncalled-for sentence, or the patient becomes confused, and rights himself almost at once. Later these lapses become more marked. In some instances these mental changes last for several weeks or even months, but they are usually not continuous. During the day the patient is commonly quite calm; it is in the evening that most of this wandering occurs. When delirium is present it is seldom noisy. The patient almost always recovers himself when his attention is called to his lapses. He does not become maniacal or boisterous—the delirium is for the most part an endeavor to get away from his surroundings.

In aortic disease these pronounced mental symptoms often come and go for six months or more before death. In mitral disease, however, once this mental attitude appears it is seldom that the patient recovers from it, even temporarily. When it is marked and persistent it is an indication of approaching death, which usually ensues in a week or two.

Henry Head has described a special form of hallucination most common in aortic disease. The patient thinks that he sees a vision at the foot of his bed. This usually takes one of two forms, either that of a veiled female figure clothed in a light gray garment, and standing near the foot of the bed, or that of a man dressed to resemble the traditional undertaker, clothed in a long frock coat, with a large, white forehead.

These hallucinations usually occur about dusk or early in the morning. That these figures do appear will be readily admitted by any one who has judiciously questioned patients with serious cardiac involvement. Their significance, however, is not so clear. They form the basis of the layman's axioms as to the approach of death; after seeing such a figure the patient often foretells the approach of the end—sometimes correctly and sometimes otherwise. Whether it is the long illness of the patient and his consequent fear of approaching death which causes him to conjure up such specters, or whether indistinct images of objects seen are not clearly pictured on the retina because of the disturbed circulation, is an open question. The visions frequently disappear on the onset of mitral symptoms.

Aortic disease in children usually takes the form of a combination of organic mitral regurgitation with aortic regurgitation. In some instances the mitral lesion predominates, in others, the aortic. In those wherein the aortic lesion predominates the early symptoms are: Pallor, nose-bleed; cardiac pain and nervousness. In those in which the mitral lesion is most marked, dyspnea occurring early and later dropsy are the main symptoms.

In adults, in the form due to arteriosclerosis, the onset is insidious, with vertigo, insomnia and cardiac pain as the outstanding features. The pain is more marked than in the rheumatic cases. The mitral valve is not as frequently involved coincidentally as it is when the disease is due to infection. The accompanying dilated arch of the aorta is more common in the arteriosclerotic cases than in the rheumatic cases.

PHYSICAL FINDINGS.—*Observation.*—One can sometimes make a snap diagnosis of aortic regurgitation on inspection, but this is the exception. It is only when the carotids throb with each pulsation and the peripheral arteries pulsate that this is at all possible. The presence of the capillary pulse is of even greater value. This capillary pulse can be seen under the finger-nails immediately after they have been pressed upon and released. It appears as an alternate reddening and blanching under the point of pressure, or it may be demonstrated by drawing a pencil across the forehead and then observing the alternate waves of red and white following its trail. It is not very usual to find it well marked. It may be stated in passing that this capillary pulse is occasionally seen in pa-

tients who have a very low blood-pressure from any cause. Here again, however, it is uncommon. One may sometimes see the arteries on the temple straighten out and pulsate. As has been shown by McKenzie this straightening out and movement to the side is due to the fact that these vessels, because of the sclerosis, are crooked and much more elongated than normally. The powerful thrust of the column of blood tends to straighten them out, and gives the impression that they move from side to side with each beat. In well-marked cases of aortic regurgitation the eyes are wide open and bulge, suggesting the onset of Graves' disease. They are bright and moist. The complexion is pale gray or sallow. When the disease is established the apex-beat is displaced downward and outward, being almost always in the sixth space or below. Usually the farther down the apex is the greater is the hypertrophy, and the farther out it is the greater the dilatation.

If the patient is under forty years, and if the disease has lasted for some time, the chest-wall over the heart bulges more than it does in the right side. Of course, when the disease begins late in life this does not often happen. Except in marked decompensation the impulse is strong and regular. The reason for the heaving impulse is that in these cases of large hearts the apex is made up entirely of hypertrophied left ventricle. When the impulse is heaving and strong, hypertrophy dominates, whereas when the impulse is diffuse and feeble dilatation is in the ascendancy. Occasionally in the case of those suffering from severe anemia or from cachexia or loss of flesh, there are marked pulsations over the base and aorta, closely simulating those of aneurysm. This is especially the case if there is marked pulsation in the episternal notch.

Palpation.—Systolic thrills over the base of the heart are frequent. The arteries feel hard, large and thickened. When one palpates the radial artery, the pulse comes up against the finger suddenly and powerfully, yet it immediately falls away, and the vessel is apparently completely emptied. The large heart has expelled a great amount of blood into the aorta, and a part of this immediately falls back into the ventricle, leaving nothing to keep up the tension in the arterial tree. This is the cause of water-hammer or Corrigan pulse. If the arm is raised this phenomenon can be more readily demonstrated to the student.

The researches of Hewlett and Van Zwalenberg have shown that much of this collapse of the pulse is due to a reflux of the blood from the peripheral arteries into the aorta. On the other hand, the absence of the collapsing pulse in aortic regurgitation does not necessarily indicate the presence of aortic stenosis, inasmuch as this type of pulse may not be present unless there is considerable reflux. The pulse is always retarded or delayed. There is a much longer interval of time between the beat of the heart and the radial pulsation than in normal patients. This varies according to the amount of regurgitation present. This delay is most noticeable when the hand is raised above the head. The Corrigan pulse is present in most of the rheumatic cases. When lues is the cause, the proportion of distinct Corrigan's is decidedly less.

Percussion.—The area of percussion dullness is increased to the left and often reaches the anterior axillary line. The upper border may reach the third rib on the left side. There is usually a slight dullness to the right of the sternum, near the base.

Auscultation.—A diastolic murmur at the base of the heart is the most reliable and constant auscultatory evidence of aortic regurgitation. This is due to a return of the blood from the aorta through the partially closed valves, after the systole of the ventricle has thrown it into the vessel, and while the ventricle is once more being filled by the blood from the auricle. The quality of the murmur depends upon the size and character of the opening and upon the pressure in the vessel itself. For that reason a small leak associated with sclerotic valves with a high pressure may cause a much more intense murmur than if a large amount of blood is thrown back through the large orifice. In any case a calcified orifice causes a louder murmur than a flexible one, which may yet be the site of a very much further advanced lesion. The murmur is of greatest intensity in one of three places:

(1) On the chest surface, at a point over the valve just as the junction of the sternum with the left third costal cartilage. Occasionally this is not the case, inasmuch as the conus arteriosus of the pulmonary artery is here placed between the aorta and the chest-wall and because its large size may interfere with the transmission of the sounds.

(2) On the right side of the sternum at the junction of the second costal cartilage.

(3) At the fourth left intercostal space at the edge of the sternum.

A frequent cause of this variance in intensity depends upon which cusp of the valve is most markedly affected. Each cusp vibrates differently, and thus transmits sounds of different intensity. The different points at which the murmur may best be heard, together with its transmission, as well as the ultimate cause in most instances, may be fixed in the minds of the observer in the following manner: An ink mark is placed over each of the points above mentioned, also over a point in the neck at which the murmur is clearly heard. If these four points are connected by outside lines, an irregular parallelogram is formed, which somewhat resembles a crude diagram of a vagina—the ultimate cause of the lesion.

In rare instances this murmur, like the murmur of aortic stenosis, is best heard just outside the hypertrophied apex in the anterior axillary line. Often it is not widely transmitted, and yet when it is very loud it can be heard all over the chest-wall. Sometimes the high-pitched faint murmurs are best heard by placing the ear against the naked chest-wall.

This murmur is, however, often overlooked, due to the fact that it is frequently so soft. It is either a blowing or a purring sound. It can sometimes be brought out by exertion; in other instances exercise makes it inaudible. Like all murmurs it may be present at one examination and missing at the next, so that one positive finding is worth a dozen negative ones. The character of the murmur varies. In the case in which it

is frequently missed it is only a mere whiff after the second sound. In other instances it is quite raucous. It is heard well down along the sternum as far as the fifth costosternal junction. In many of the cases due to arteriosclerosis it is not transmitted into the vessels of the neck. Having the patient sit up and bend forward often serves to bring out the murmur. An aortic systolic murmur is present in approximately one-half of these cases. Sometimes one hears this systolic murmur at the base, in the course of aortic regurgitation, and yet on postmortem examination no stenotic or sclerotic changes are found. This has been explained as being due to the fact that at the beginning of ventricular systole the regurgitant flow has not entirely ceased, and when this latter flow meets the opposing current a murmur is produced which is systolic in time. When aortic regurgitation occurs in children it is quite common to find also a systolic murmur present at the apex, due to a coincident mitral regurgitation. The first sound of the heart is loud and long, due to the great quantity of blood which is thrown out in systole. The murmur is usually present at the end of the second sound. Sometimes, however, it occupies the entire diastole.

According to Broadbent, the long, loud diastolic murmur shows that considerable pressure is kept up by the aorta; it is a sign that hypertrophy is present, and that the leakage is not very great. On the other hand, a weak, short murmur shows that the heart is weak, and is, therefore, a bad sign. When dilatation occurs the first sound at the apex is superseded by a systolic murmur, which is due to a relative mitral insufficiency. When dilatation has been overcome this murmur disappears and a clear first sound reappears.

In about one-third of the cases the first sound at the apex is vigorous and somewhat resembles the slapping sound present in mitral stenosis. The protodiastolic gallop rhythm is frequently heard in aortic regurgitation, especially when there are evidences of broken compensation.

FLINT MURMUR.—Austin Flint described a murmur that is frequently present in aortic regurgitation, and is identical in time and character with that of mitral stenosis, and can scarcely be differentiated from it. Flint believed it to be due to a functional mitral stenosis, and this theory has thus far not been seriously controverted. It is more commonly found when the aortic regurgitation is due to rheumatic fever than when lues is the cause. It is more fully discussed under mitral stenosis.

EVIDENCES OF AORTIC REGURGITATION OUTSIDE THE HEART.—Frequently a coincident stenosis is present, or at least there is a roughening of the aortic valves, causing an aortic systolic murmur, which is transmitted up to the vessels of the neck. In the larger arteries a to and fro murmur is frequently present. It is best heard over the femoral artery and is known as the murmur of Duroziez. This phenomena is believed to be due to low diastolic pressure. When the stethoscope is placed over the femoral artery, and pressure exerted, a sharp systolic sound (pistol shot) is sometimes heard. This is a local phenomenon and may be heard to a lesser degree in many other conditions.

SPECIAL EXAMINATIONS.—*Sphygmograph.*—The sphygmographic tracing is characteristic. The up-stroke is high and almost perpendicular, and forms a very acute angle with the sharply descending down-stroke.

From a diagnostic standpoint exact measurement shows that the diastolic notch in the collapsing pulse falls below the middle of the pulse-wave, while in the normal and anacrotic pulse it lies above the middle of the wave (Hirshfelder). To put this in other words, in the Corrigan pulse over one-half of the fall of pressure occurs during systole, while in normal pulse the fall occurs chiefly during diastole.

Blood-pressure.—The blood-pressure is regularly high in the patient presenting symptoms; it is rare to find it below 160 Hg. The pulse-pressure is usually about 100. In fact, when one takes a blood-pressure measurement by the auscultatory method a tapping sound is often heard until the mercury goes down to zero, so that the diastolic reading must be taken by the oscillating method. When the patient is in a recumbent posture, the blood-pressure in the leg is from 50 to 100 mm. higher than it is in the arm, and this fact has considerable diagnostic value.

Electrocardiograph.—The evidence of left-sided hypertrophy is an extremely prominent S-wave in lead 3, whereas the R-wave in lead 1 becomes larger than the R-wave in lead 2.

X-ray.—The outline in aortic valve diseases is more constant than it is in mitral lesions. The region about the apex is enlarged and obtuse. The apex itself is out near the axillary line. The body of the left ventricle is egg-shaped. This is called the duck-heart, because of its resemblance to a sitting duck.

Fluoroscope.—One of the usual accompaniments is the aortic fling, i.e., the underexcursion of the aorta during beats, which is a very striking phenomenon. In severe cases it closely resembles the picture of aneurysm and is commonly diagnosed as such when read from a single x-ray plate. There is also a sharp left ventricular contraction with a distinct lifting motion about the region of the apex. In uncompensated cases this movement appears to be separated from the rest of the ventricle.

Diagnosis.—The diagnosis of aortic regurgitation is commonly not difficult. However, there are five conditions which may occasionally cause trouble: (1) the murmur of mitral stenosis; (2) the Flint murmur; (3) the Graham-Steele murmur; (4) pulmonary insufficiency (see Diagnosis under Mitral Stenosis); and (5) aneurysm.

Of these only mitral stenosis causes any great difficulty. This becomes particularly noticeable when the murmur of mitral stenosis is diastolic in time rather than presystolic. The Flint murmur, when occurring at the same time, may be a disturbing factor, especially when it is loud and the aortic murmur is soft and indistinct. A third, confusing murmur is the so-called Graham-Steele murmur which accompanies the murmur of mitral stenosis. It is heard best along the left sternal border and is not transmitted down to the apex.

When one of these three murmurs is present and its limitations are not strictly defined, we are most likely to establish the diagnosis on the

basis of the peripheral signs, such as: Corrigan pulse; blood-pressure changes in arm and leg; pistol-shot sound; Duroziez murmur; and a history of rheumatic fever or of syphilis.

DIFFERENTIAL DIAGNOSIS.—In the presence of a well-marked throbbing of the vessels of the neck, with few other characteristic signs, the question of the presence of *aneurysm* is frequently raised. Many of the symptoms are the same in both diseases, *i.e.*, the pain in the chest, the cardiac hypertrophy and the history of lues are similar in both. In aneurysm there is usually a systolic murmur, but often there are both systolic and diastolic murmurs. In these doubtful cases, in which there is no characteristic aneurysmal bruit, the most distinctive auscultatory sign is a sharply accentuated clanging, second aortic sound. The more plainly this sound may be heard away from the second right costal cartilage, the greater becomes its diagnostic import, as proving the presence of aneurysm. Of course, in the presence of other characteristic signs, such as tracheal tug, marked dullness at the base, inequalities of the pulse, thrill, etc., there is little trouble in arriving at a conclusion. The frequency with which the two lesions are coincident must always be kept in mind, and in every case of aortic regurgitation one should consider the possibility of a concomitant aneurysm. However, aneurysm is more commonly complicated by aortic regurgitation than *vice versa*. Finally, in all cases in which there is any doubt either as to diagnosis or as to the presence of both lesions fluoroscopy is the court of last resort.

Some clinicians describe a functional aortic regurgitation due to dilatation of the mouth of the aorta, or occurring as an accompaniment of *pulmonary insufficiency*. Among the rarer disturbing conditions, from a diagnostic standpoint, is *severe pernicious anemia*, which produces murmurs at all orifices; these are especially marked over the great vessels and sometimes produce a pseudo-collapsing pulse. Another rare diastolic murmur is sometimes heard over old pericardial adhesions.

Mediastinitis, because of adhesions about the vessels, produces a cardiorespiratory murmur which may be confusing. It is loudest during inspiration and often disappears with change of posture.

Rupture of the valves is recognized by the sudden onset of symptoms after severe exertion. There is pain, a tumultuous action of the heart, and a loud diastolic murmur.

Treatment.—This is the disease of the heart above all others wherein **careful living** and avoidance of extremes are of most importance. Nowhere else in cardiology is the regret of "what might have been" more properly applied, because a single rash act may precipitate a fatality, whereas with care the same individual might have lived many years. These accidents are most apt to happen shortly after the inception of the lesion, before the heart has enlarged sufficiently to overcome the likelihood of sudden dilatation. This of course obtains only for those cases which occur following the infections, particularly rheumatic fever. When it follows syphilis or arteriosclerosis the onset is so slow and so insidious that little good can be accomplished by rest in bed for a prolonged period.

The patient who suffers from aortic disease must be especially **warned against a sudden exertion of any kind**, because of the possibility of sudden death. It is of course needless to say that one should not warn such a patient of the likelihood of sudden death. However, his friends should be warned of the possibility, and it should be impressed upon the patient himself that every such act will render his condition irretrievably worse. Oddly enough such patients do not usually die at the time of the excitement, but during the hours and days following. These aortic patients are particularly apt to have very positive views and are with difficulty restrained. Such patients should take vacation every few months, and during this time should remain in bed for three or four days.

If at any time there is a change in the character of the pulse or extension outward of the apex-beat, **absolute rest** must be enjoined for a month at least.

When these aortic cases present such urgent symptoms as severe pain and dyspnea, sudden death is at any time a probability.

If one divides the causes of aortic disease into rheumatic fever, arteriosclerosis and syphilis, it will be seen that there is little hope of permanent cure or satisfactory medication except in the last group. And even here miracles cannot be performed.

There are no specifics for the rheumatic group, although **salicylate** will occasionally relieve pain and some of the minor symptoms.

In the arteriosclerotic group the use of **potassium iodid** is of undoubted service both in lessening the progress of the disease and in alleviating the symptoms. In those cases which are due to syphilis, repeated courses of small doses of **salvarsan** are indicated. Certainly every such patient should have one or more courses every year at least. In the absence of this, one must resort to yearly courses of **mercury** or potassium iodid, even if there are no symptoms whatsoever. The presence of active symptoms, naturally, calls for more frequent use of these agencies. One can never imagine a luetic lesion of the valve as being stationary. When symptoms occur, such as pain and dyspnea, potassium iodid is of value in itself in relieving the symptoms. **Digitalis is not indicated** in aortic disease unless there are evidences of broken compensation. For the relief of the symptoms—and these are usually of a nervous character—sedatives for the nervous system are indicated; **bromids** in 20 or 30 grain (1.3 to 1.95 gram) doses three times a day are efficacious for the relief of the milder symptoms. When sleeplessness and palpitation are marked, one must often resort to **chloral** or some other hypnotic. **Morphin**, however, is the sovereign remedy, and does more to prolong the lives of these patients than any other single medicament. They must have sleep, and a hypodermic of morphin is the best means of producing this result. Sometimes small doses of morphin and chloral by mouth act better than a large dose of either.

When the evidences of mitral failure are apparent, such as edema, enlarged liver, etc., then the case must be treated along the lines of mitral

disease, with this exception, that as soon as compensation begins to improve, the dose of digitalis must be reduced.

Prognosis.—The outlook depends upon (1) the cause of the lesion, (2) the stage at which it is discovered, (3) the extent of the circulatory changes outside of the heart, and (4) the extent of involvement of the other valves.

In adults, if the lesion is due to a rheumatic endocarditis, the outlook is favorable. It is not very much worse than that for uncomplicated mitral disease, provided the blood-pressure is low and the apex is within the nipple line. After an acute attack of rheumatic aortic endocarditis, it is no rarity to find a well-marked Corrigan pulse, a pulsating aorta, and hypertrophy with no distinctive symptoms, and yet these patients may live for decades in apparently good health.

In the case of a patient under twelve years of age, the outlook is not favorable because of the likelihood of the development of a fresh attack of endocarditis. Especially is this true when, as is so often the case, there has been a coincident involvement of both mitral and aortic valves. Here the added likelihood of the development of malignant endocarditis at a later period should always be kept in mind. When the disease is the result of atheroma the eventual outlook is worse than when it is due to any other cause, because the lesion is always a progressive one. This progression may, however, be a matter of many years, and the prognosis must be based upon the length of time it has existed when discovered. If the disease is relatively early there is little immediate danger, and serious events may not occur for five or ten years. The progressiveness of this basic lesion rather than the involvement of the valve itself is particularly dangerous. It almost always involves the coronary vessels and their orifices, and is thus responsible for more of the anginal attacks and sudden fatalities than is the valvular lesion itself. This stenosis frequently involves the kidneys also, and not infrequently kills through these organs rather than through the heart itself. This type is associated with sudden death more often than with the case, due either to rheumatism or syphilis. It is a particularly serious form of the disease in young people, inasmuch as here the progress is more rapid than in the aged. This progressive arteriosclerotic process in young people is sometimes a family trait, and when this is the case, other things being equal, the age of death will be approximately the same as that of the ancestor. The most frequent cause of aortic regurgitation is syphilis, and here the outlook depends upon the adequacy of treatment, the time of discovery of the lesion, and the time of the appearance of symptoms. In approximately one-half of the cases of syphilis there is some involvement of the heart, yet it is frequently not made evident by the appearance of any physical sign. These changes usually take place in the acute stage, and the results are not noticeable until years after. The lesion is generally discovered only on examination for some symptoms of cardiac failure. In the ordinary hospital case this is, on an average, fifteen years after the appearance of the initial lesion. Such patients, as a rule, only

take treatment until the disappearance of the secondary symptoms, or, on an average, about three months. Occasionally the lesion is discovered during an examination for life insurance in one who is free from symptoms, and here treatment materially improves the prognosis. Yet even here twenty years seldom pass between the appearance of the lesion and cardiac failure. In the case of patients who present themselves for the first time after symptoms have appeared, life is seldom prolonged more than three years, in spite of treatment. Usually death occurs in less than one year if the presenting symptoms are very marked. Unquestionably treatment alleviates some of the symptoms, particularly the anginoid pains, but it seldom produces the marvelous results which are obtained elsewhere in the body by specific medication. Once the murmur of organic aortic regurgitation is present it never permanently disappears. In general a long, loud murmur is better than a short, faint murmur. A harsh second aortic sound heard in the vessels of the neck independently of the murmur shows that the leakage is slight and that the outlook is good. The presence of the Flint murmur does not materially affect the immediate prognosis, although it shows that the disease is relatively far advanced. The more collapsing the character of the pulse the greater the regurgitation, and, with the exception of the cases which are due to rheumatic fever, the worse the prognosis. On the other hand, without this collapsing pulse the presence of uncomplicated aortic regurgitation is not very grave. When combined with aortic stenosis the absence of the collapsing pulse is not necessarily hopeful. When a well-marked collapsing pulse has once been present and then disappears the outlook is bad. When the blood-pressure, either systolic or diastolic, is not markedly raised, and the pulse is normal in frequency, the outlook is good. If the blood-pressure is elevated, but does not steadily rise, the outlook is favorable for the time being. A marked fall in blood-pressure is ominous. When the pulse becomes permanently rapid without any appreciable cause the eventual outlook is serious. When it remains at 90 or above and does not react to ordinary measures and to digitalis, the progress is generally intermittently downward. Not infrequently we find the pulse quite good continuously up to the minute of death, or even better than it has been for weeks previously, but usually this is not so, and it is decidedly weaker, even though it is regular on the last day or two of life. When the patient presents himself, some of the symptoms of added mitral disease are generally present, and the more marked the evidences of mitral decompensation the worse the outlook. In aortic disease, except the form due to rheumatic fever, the patient seldom recovers temporarily from more than three breaks in compensation, whereas in primary mitral disease recovery may follow many attacks which threaten life. Once pulmonary stasis occurs the patient seldom recovers. Attacks of severe dyspnea in aortic disease are of much greater consequence than in mitral disease, because they mean at best a functional mitral regurgitation which is equivalent to a weakness in the ventricular wall. Such attacks are frequently the beginning of the end. When auric-

ular fibrillation occurs in aortic disease, unless aortic disease is due to a rheumatic infection, it does not react to digitalis, and the progress of the disease is steadily downward. As in all forms of cardiac disease the outlook is better for women than for men. Sometimes, when aortic regurgitation is met with in youth, and is quite severe and progressive, and an early fatal termination seems inevitable, the disease will apparently cease its progression on the addition of the murmur of aortic stenosis producing the seesaw murmur, and the patient may live for years. Most of the sufferers from aortic disease die as the result of an intercurrent disease, and the majority are associated with a functional mitral regurgitation during the terminal infection. Many die of one of the sequelæ of syphilis or of arteriosclerosis in other parts of the body. Attacks of anginoid pains, rapid weakening of the heart-sounds, with a pericardial friction rub at the base, are not uncommon, and usually indicate death within a few days. Mental aberration is particularly common toward the end of the progress of aortic regurgitation. An extra systole, not previously present and not due to digitalis medication, is sometimes a harbinger of the end. Angina pectoris and acute suffocative pulmonary edema are frequent terminal events. Death in angina pectoris usually occurs at the beginning of the attack rather than at the end. Death is not so common in the severe and prolonged attacks of angina pectoris, but the patient often dies a day or two after the attack. In such cases the frequency of the heart increases, pressure falls, and pulmonary edema follows. The angina apparently acts as a sort of reflex inhibition on an already damaged organ. As a rule patients suffering from aortic regurgitation are in and out of bed until the last few weeks of life, and death is unexpected. Sudden death is more common in patients suffering from this than from any other valvular lesion. The atheromatous patients are particularly apt to die in this manner. On the other hand, the rheumatic cases seldom die suddenly. Sometimes death occurs during sleep; commonly, however, it follows after or during some strenuous exertion. It happens most commonly in those who have not complained of any decided symptoms and who consider themselves quite well. It occurs not infrequently during sexual intercourse. Thus, each year, the city papers record the fall of some country church pillar who has died in the arms of an urban Delilah.

Pathology and Pathological Physiology.—The pathology varies somewhat with the cause. In the cases due to syphilis there is an arteritis of the fine vessels at the base of the valve. This produces degenerative changes that are to be seen as plaques, the size of a pinhead and larger. Their color varies from pink to gray and yellow. They consist microscopically of an infiltration of the subendothelial tissue with layers of round- and spindle-cells. In these cases this process is not confined to the valve alone but is apt to involve the openings of the coronary orifices, finally occluding them, and often extending down the vessel itself. This probably is the reason for the frequency of angina pectoris in syphilitic cases. In other cases the scar tissue produced by the lesion

in the valve contracts and produces varying deformities. This is most commonly the result in those cases which are due to infection. The edges are curled back or become adherent, calcification takes place so that the valve can not come into apposition during diastole, and a leak results. The amount of leakage depends upon the degree of this faulty apposition and upon the tonus of the cardiac muscle, which attempts to overcome the leakage. Because of this irregularity and rigidity of the segments there is of course also some stenosis. In the arteriosclerotic cases there is a gradual thickening of the cusps which become hardened and retracted. In these cases also there is often, but by no means always, a general involvement of the arch of the aorta and of the coronary orifice. Here again this is a frequent cause of the painful anginal attacks. The cases due to endocarditis usually occur in youth, there is no involvement of the aorta itself, nor of the coronary orifice, and the disease is not progressive unless there is a fresh attack of endocarditis. As a consequence of the back pressure which is gradually produced, the heart becomes able to adapt itself to the greater amount of work and consequently hypertrophy results. This produces the greatest enlargement of the heart that is ever met with. It is frequently called the beef heart because of its resemblance in size to that of a cow. The researches of Stewart have shown that there is also another factor in the production of this hypertrophy. As is well known, unstriped muscle always reacts to a stimulus. In the heart it is ordinarily the stimulus which follows the distention of the ventricle resulting during diastole. In regurgitation there is some distention almost immediately after systole, so that the tone of the muscle of the ventricle is almost constant throughout nearly the entire cardiac cycle, and consequently an hypertrophy of the muscle is developed. In the latter stages, either because of greater reflux or because of degeneration of the hypertrophied muscle, the ventricle gradually enlarges and thus separates the base of the mitral valves, causing a space to exist between their free edges. A relative mitral insufficiency is the result. Of course, after this occurrence all of the phenomena of broken compensation are in evidence. The extra effort of the ventricle to expel the blood which flows in during the diastole from the mitral orifice and that which is regurgitated from the aorta causes a high systolic pressure in the arteries. The instantaneous regurgitation of the blood after its expulsion accounts for the sudden drop of the column of blood, and this produces a low diastolic pressure; consequently the pulse-pressure, *i.e.*, the difference between systolic and diastolic pressure, is very high. When these alternate high and low pressures are kept up for a long time, a general arteriosclerotic change takes place.

MITRAL REGURGITATION

Etiology.—This is by far the most common valvular lesion met with in practice. The mitral regurgitant murmur constitutes 50 per cent. of all of the simple, uncomplicated organic murmurs heard. If combined

lesions are counted, it is present in more than two-thirds of all the patients suffering from chronic endocarditis.

The distinction between organic and relative, or functional incompetence, must be made more commonly in this disorder than in mitral stenosis. In fact, diastolic murmurs are rarely functional, whereas systolic murmurs are frequently due to functional or relative incompetence, or are accidental.

The mitral organic murmur is in most instances due to a previous chronic endocarditis. Certainly in patients under twelve years of age, if fetal abnormalities and chorea can be excluded, all cases of endocarditis may be considered as due to rheumatic fever. In these patients the presence of two large central incisor teeth in the upper jaw are strikingly suggestive. They are called tombstones. People who have these prominent teeth appear to be more likely to contract the rheumatic infection than are others. In a child the term "tombstones" for such teeth is quite appropriate; it suggests the sequelæ; *i. e.*, rheumatic fever, endocarditis, death, and tombstone.

Mitral disease is synonymous with rheumatic fever in adult life, up to forty years of age. The exceptions to this rule are extremely few. When the onset is after fifty years of age a large proportion of cases are due to arteriosclerosis; very exceptionally does one meet with incompetence due to trauma such as follows rupture of the chordæ tendineæ from exertion.

Relative incompetence is quite common. It is accountable for the murmur sometimes met with immediately after severe exertion or during severe infection and wasting disease, tuberculosis, chronic nephritis, myocarditis, and in the course of aortic regurgitation. The distention of the chambers of the heart separates the bases of the valves, and this must necessarily separate the edges of the valves, thus allowing some regurgitation.

On postmortem examination the evidence of such a relative incompetence can seldom be demonstrated. Roughly speaking, about one-half of such murmurs disappear after a short interval.

Symptomatology.—GENERAL SYMPTOMS.—While it is true that each form of chronic valvular disease presents some symptoms which are peculiar to itself, practically all forms sooner or later present the mitral regurgitant and tricuspid syndrome in their terminal stage. The early distinctive symptoms of mitral regurgitation which are commonly linked up into those of mitral stenosis have to deal with stasis in the pulmonary circuit, and are: (1) cough, (2) dyspnea, and (3) other respiratory disorders, such as hemoptysis, all of which are primarily due to left heart-failure, whereas the later symptoms of this lesion, as well as of all forms of chronic valvular disease, as (1) cyanosis, (2) enlargement of the liver, and (3) a gradually ascending edema, are due to right heart-failure. Most patients suffering from mitral regurgitation experience a number of minor complaints for a long time before consulting a physician. These are due to various minor circulatory changes, often

of a transient nature, the pathology of which is not always clear. Weakness is the earliest of these symptoms to appear. Its onset is usually so gradual that the patient is afraid of being accused of laziness, and this he feels keenly. In other patients it is only noticed after severe exertion. This weakness must not be confused with the nervous trembling and dyspnea which, in normal people, follows unusual exertion. The sense of inability to do work of any kind, whether it is mental or physical, often appears to an onlooker to be a mental as well as a physical fatigue. The patient's commonest complaint is that he cannot drag one leg after another, especially at the end of the day. Another form of the same symptom is a feeling of fatigue in the throat at the end of the day. The patient feels as though he had talked too much. In fact, all cardiac symptoms are end-of-the-day symptoms. Of course this sense of weakness and fatigue is not pathognomonic of cardiac disease, for it is met with in many other disease conditions; but when it occurs for the first time in a middle-aged person it is always a suggestive symptom.

Another evidence of such congestion is the slight cardiac cough. It is apparent during exertion when climbing a hill, going out into the cold or beginning a conversation. It is different from an ordinary catarrhal cough in that as a rule it is not repeated. The patient is usually not conscious of this. Increased sensitiveness to cold is not a frequent complaint. However, nearly all patients with cardiac involvement feel worse in cold weather. Palpitation and a sense of powerful heart-beat are sometimes complained of, but this is a complaint more commonly present in those who are free from heart disease.

An early result of circulatory disturbance in mitral regurgitation is stasis in the capillaries of the lung, and this is the ultimate cause of dyspnea. For that reason shortness of breath is the earliest subjective evidence of mitral regurgitation. This stasis does not occur provided the left ventricle is strong enough to prevent it; for that reason it is not present in any case until there is some failure of the ventricle—either because the leak is too large or the ventricular muscle too weak to overcome it. When there is any severe strain, such as results from unusual exercise, it becomes apparent. This explains why many patients do not show the slightest evidence of dyspnea, even though the murmur is very pronounced. Every one has met with such cases in athletes or in very strong, vigorous people who, on being examined for other purposes, are found to have pronounced mitral disease which must have been in existence for years without producing the slightest symptom of any kind. These cases, however, must be regarded as the exception rather than the rule. After existing for a longer or shorter period the continued pressure in the capillaries of the lung causes changes in the vessel-walls and in the surrounding tissue which favor the production of a chronic bronchitis, thus still further increasing the dyspnea.

There are many patients who never show any other symptom than dyspnea until near the end. Those who present symptoms earliest are

those who have had endocarditis in childhood. Relative insufficiency, such as that resulting from fever or anemia, seldom gives rise to any symptom except dyspnea on exertion and a sense of weakness. Inorganic heart disease, and later the attacks of dyspnea which formerly occurred on climbing a hill, going out in the cold, or facing a wind, or following any unusual exercise, and which quickly subsided, fail to stop so quickly, because the reserve power has been used to its utmost. These attacks now come on in the middle of the night while the patient is asleep, and their occurrence is not in any way casually related to physical exertion. Often there is associated with these attacks a desire to evacuate the bowels, also a belching, which the patient believes gives him relief.

Just why cardiac patients have these night attacks has never been satisfactorily explained, because it is not due, in the majority of instances, to dreaming, nor to indigestion. In the advanced cases in which dyspnea follows immediately after falling asleep the ultimate cause is a diminished sensitiveness of the respiratory centers which allows carbon dioxid to accumulate more readily than when the patient is awake.

The patient is first restless, then he breathes with very shallow inspirations, and finally forgets to breathe at all. Then he wakes up with a start and has a paroxysm of rapid breathing associated with terror, which makes him still worse. Often this happens just as he is falling asleep. Oppression on the chest during this paroxysm is the chief complaint. The recollection of such spells causes the patient to try to stay awake sooner than go through this terrible ordeal at night. The loss of sleep in its turn reacts badly on the sick one, aggravating his condition; finally the dyspnea occurs during the day on the least exertion.

When the disease has advanced to the point where the patient must sit up in bed in order that he may breathe without distress the condition is termed orthopnea. This orthopnea is characteristic of cardiac disease, and has some diagnostic value. In no other disease, with the possible exception of aneurysm, is it so necessary for the patient to sit up in order that he may breathe. One may occasionally make a diagnosis on entering a ward or the sick room, on the basis of this phenomenon. The least attempt on the part of the sufferer to lower his head is followed by a distressing dyspnea; in fact, his progress toward recovery may often be measured by the gradual diminution of the number of pillows necessary for his comfort. This orthopnea is often developed within a day of the onset of decompensation. It is perhaps the most serious of the major symptoms.

Susceptibility to attacks of bronchitis, particularly during the winter months, is the rule in mitral cardiac cases of long standing. These attacks last so long, and are so resistant to treatment, that the laity are often alarmed as to the likelihood of the onset of pulmonary tuberculosis. A loss of flesh, slight rise in temperature and cough with bloody

expectoration form a picture which is indeed strongly suggestive of tuberculosis. When dyspnea becomes a marked symptom, other evidences of venous stasis due to right heart-failure usually appear. Sharp pain is uncommon in mitral regurgitation unless stenosis is also present; on the other hand, uncomfortable sensations about the heart, and tenderness of the skin over it, are frequently present. The patient and physician commonly ascribe these to the indigestion so often accompanying cardiac disease. The evidences of right heart (tricuspid) failure must be considered as part of the mitral regurgitation, inasmuch as they are almost always a direct sequence or concomitant of it. A slight cyanosis sometimes appears before there are any other signs, due to peripheral stasis, and produces a bluish tint of the cheeks and ears. If this lasts sufficiently long it is associated with the clubbed fingers which are always so suggestive of circulatory disease. The terminal phalanges appear as though they had been crushed back with a hammer, and usually are different from those due to pulmonary disease, which are enlarged but of an almond shape. These distinctions are not always definite and clear-cut, for pulmonary and circulatory diseases are often combined; but they frequently suggest that one or the other of the organs is the cause of the deformity.

The first symptom which really frightens the patient is edema. The word "dropsy" is associated in the mind of the layman with "Bright's disease and death." Unless it is absolutely necessary to warn the patient as to the seriousness of his condition, the term "dropsy" should not be used in his presence.

Edema of the legs is due to failure of the right heart and not of the left. In nearly all cases of cardiac failure it is present at some time or other, but it is preëminently a mitral symptom. The ultimate cause of this edema is a debatable question, but a large part of it is due to a local stasis, and it begins where circulation is most retarded. This is in the dependent portions of the body when the patient is up and about.

This slowing of the circulation is of course manifest at first only during the latter part of the day when the cardiac weakness becomes evident, disappearing after the night's rest and the equalization of the circulation. After the edema has disappeared in the morning, pressure over the former edematous region is exquisitely painful and is a sign of some value, showing that edema has been present. Later, as the weakness and leakage of the right auriculo-ventricular valve increases, it becomes continuous and gradually moves up the legs to the abdomen. This progression is quite different from the edema occurring in nephritis, where the edema is due to a toxin, and where it is quite as bad at one time as another and is generally universal. Even here, however, sooner or later the heart is involved, and the edema is worse in the dependent portions of the body.

When the edema has extended to the thigh, ascites is the rule. It is, however, not always demonstrable.

It is very rare, in mitral regurgitation, for ascites to precede edema of the legs, and in any case in which this happens one must look for other causes of the ascites. The same holds true with hydrothorax.

While ascites is a serious symptom, the patient often recovers from it entirely and may live for years thereafter. When ascites can be demonstrated, right-sided hydrothorax is generally also present. When fluid can be demonstrated reaching up to the angle of the scapula it should be removed, as it is a distinct menace to the patient. This hydrothorax affects the right side in preference to the left, because of the anatomical position of the major azygos vein which drains the intercostal spaces and pleura. The vein enters the superior vena cava at an oblique angle, and thus the least pressure of an enlarged right heart produces an obstruction. The hydrothorax increases the work of the heart by pressing on the right lung and by pushing the heart further to the left. Another explanation is that it is due to postural edema, the patient usually lying on the right side. It is an occasional cause of sudden death.

At about the same time that the edema is marked the liver becomes noticeably enlarged, and is the first *palpable* evidence of broken compensation, just as the presence of fine subcrepitant râles at the base of the left lung, when the patient sits up after having been on his back for some time, is the first definite *auscultatory* evidence of failing compensation. The liver is large, smooth, hard, and has rounded edges. It is often a hand's breadth below the margin of the ribs. Following the early breaks in compensation it almost always recedes and cannot then be palpated during the interval. This recession of the liver is a good omen. After repeated breaks in compensation it becomes permanently hard and enlarged. A slight icterus, not a well-marked jaundice, but rather a muddy complexion, is commonly also present. The whole clinical picture of icterus, enlarged liver, and dropsy, when seen for the first time, closely resembles a case of cirrhosis of the liver and is frequently so diagnostic. A dull pain over the epigastrium is a very common complaint. This is due to cardiac dilatation and to enlargement of the liver, and is a comparatively late symptom. Digestive disturbances due to concomitant venous engorgement of the digestive tract are commonly present quite early; yet in many cases they do not appear until anasarca is quite general. Among these the earliest is belching and a sense of fullness after meals; later on there is anorexia, and, as the case progresses, vomiting is commonly present. Often this vomiting is mistakenly thought by the patient and physician to be due to medicine ingested. In some cases periodical diarrheas occur.

KIDNEYS.—About this time the urine is much diminished and presents all the signs of passive congestion, that is, a small amount of albumin and hyaline casts. Sometimes it is difficult in the first few days to differentiate such a urine picture from that of the concomitant nephritis.

Indeed, in all moderately advanced cases of cardiac disease, a trace of albumin, and hyaline casts, are commonly present in the urine at the end of the day.

Because of the extensive edema, it is often difficult, when the patient is first seen, to determine whether one is dealing with a primary cardiac lesion, with edema, due to passive congestion, or to a primary renal lesion with secondary cardiac changes, or to a combined cardiac and renal disease. It is uncommon to find large amounts of albumin for more than a day or so in patients with uncomplicated heart disease. Usually only a trace of albumin is present, no matter how severe the edema may be.

Granular casts are not common in the severe cases of passive congestion of the kidney secondary to cardiac disease, while they are the rule in kidney disease. In the presence of marked decompensation the pthalein test is of no help in making the differentiation from true renal disease. However, after a few days of rest and treatment the output approximates the normal in the cardiac cases, whereas there is little change in the nephritic cases.

In the cardiac cases, the sodium-chlorid excretion is only slightly interfered with, so that restriction of salt in the diet does not produce the marked results that it does in the edema of nephritis. In the primary cardiac cases, the blood-pressure is commonly low, whereas in the majority of renal cases it is high.

In many patients the minor symptoms, with perhaps a little shortness of breath on exertion, are all that are noticed for years. Every now and then, however, usually as the result of an acute infection or of some sudden severe exertion, the symptoms are exaggerated, and some of the more grave complaints are added, even threatening life itself. These complications are usually evident in the shape of a severe bronchitis, bronchopneumonia, or pulmonary edema. Under rest and treatment the attack is recovered from and the patient is apparently as well as before. Repeated similar attacks with minor symptoms during the interval constitute the life history of such patients, yet years may intervene between attacks. Finally some of the major symptoms persist during the interval, and then the progress is steadily downward.

PHYSICAL FINDINGS.—*Inspection.*—The mitral facies will be described under Mitral Stenosis. The precordium is prominent in children, and if the disease is of long standing, the same is true of adults. The area of the apex-beat is commonly enlarged; at a later period it becomes diffuse. It is a more extensive impulse than is present with any other cardiac lesion, not excluding aortic regurgitation. It is usually dislocated to the left, and downward. Sometimes there are visible pulsations close to the sternal border on either side; at other times the whole chest throbs.

After dilatation of the right ventricle occurs there is generally a pulsation in the epigastrium, while at the same time pulsations are visible in the cervical veins. In old people and in arteriosclerotic cases these extensive pulsations are not commonly met with. In cases due to rela-

tive insufficiency the evidence of dilatation as shown by the projection of the apex-beat is not prominent. It may be scarcely noticeable outside of the nipple line. When there is evidence of broken compensation, there is also marked dilatation of the jugular bulb above the right sterno-clavicular junction.

Palpation.—The impulse is heaving. A systolic thrill is sometimes felt, particularly in children, but is relatively infrequent. If auricular fibrillation is present the beat is, of course, irregular. The pulse and apex-beat are much in accord both as to strength and regularity; the pulse is usually small, easily compressible, and regular unless auricular fibrillation is present, in which case it becomes rapid and irregular. The number of beats which are counted at the wrist is much smaller than the number of beats counted with the stethoscope. This is known as *pulse deficit*.

Percussion.—Dulness is increased to the left, often over as far as the anterior axillary line, and to the right as much as one inch to the right of the sternum. But such an enlargement is unusual. The cardiac dulness is increased more laterally than in the vertical direction. In most cases that are well advanced, the upper border of cardiac dulness commences about as high as the third intercostal space. This upward extension of dulness is due to enlargement of the conus arteriosus of the right ventricle.

Auscultation.—The diagnosis of mitral regurgitation is commonly made on the basis of auscultation. At the point of the apical impulse there is a systolic murmur which may either follow or entirely replace the first sound. Its character varies, but it is frequently a blowing murmur. The murmur can usually be traced outward toward the axilla. It is transmitted to this region because the vibration is transmitted through the papillary muscles of the left ventricle down to the apex, thus making a solid conducting medium down almost to the chest-wall, and as the tip of the left ventricle is nearer to the surface in the axilla than on the front of the chest-wall. Theoretically it should be easily possible to hear the murmur better here than in front. Sometimes it is well heard at the middle of the posterior border of the scapula, the sound being then transmitted by the vertebræ from the base of the ventricle. In other cases it may be better heard to the right of the nipple line than at the apex. These variations in the intensity of the murmur are due to the varying contents and relations of the structures in the individual chests. In some cases the lung covers portions of the heart which are usually exposed, or again the bony framework presents some anomalies which interfere with conduction.

The pulmonary second sound is accentuated or frequently reduplicated. It is best heard over the second interspace at the left edge of the sternum.

When there is a failure of compensation one often hears another murmur at the same time over the lower part of the sternum. This is due to tricuspid regurgitation. It is softer than the mitral murmur.

SPECIAL EXAMINATION. — *Blood-pressure.* — In uncomplicated cases there is nothing characteristic in the blood-pressure. Very frequently it is lower than normal.

Pulse-tracing. — There is nothing characteristic in the pulse-tracing of uncomplicated mitral regurgitation.

Electrocardiogram. — In uncomplicated early cases there is no information to be obtained. When evidences of failing compensation are present, signs of right side hypertrophy are also found because the R-wave in lead 1 is directed downward instead of upward as is the case in normal individuals.

X-ray Findings. — In early compensated cases the x-ray shows a uniform smooth circular enlargement to the left. Later it is often oval in shape. In advanced disease the picture is fairly typical. The arch of the aorta is frequently pronounced, but the rest of the heart is globular. It is an ovoid in which the longest axis lies diagonally.

Diagnosis. — One frequently meets with a patient who presents a group of general symptoms indicative of no local or specific disease, such as increased temperature, headache, dyspnea, cough, muscular pain, etc. On making a physical examination, a mitral regurgitant murmur is discovered, and because of character, transmission, and history of previous rheumatic fever, it may be considered to be a true organic lesion. The question arises as to whether the symptoms are due here to fresh attack of endocarditis, with broken compensation, or to another disease, the mitral regurgitation being coincident. This is often a difficult problem. If on auscultation one finds behind the left scapula a large number of fine crackles after the patient has been lying on his back, or, if, on slight exertion, there is manifest dyspnea which was not previously present, and if we can exclude pneumonia and pleurisy, we are justified in considering that the symptoms are due to the valvular disease rather than to some other general disease. Usually, if the heart is at fault, close questioning will show that there have been other minor symptoms in the immediate past. In general, mitral regurgitation is likely to be mistaken for (1) pulmonary tuberculosis, (2) neurasthenia due to any cause, (3) cirrhosis of the liver, (4) chronic nephritis. The latter two have been discussed previously under Symptomatology. When the murmur is so faint that it cannot well be heard the disease is not infrequently mistaken for *pulmonary tuberculosis*. The early symptoms of both diseases are similar: dyspnea on exertion, digestive complaints, slight cough, clubbing of the fingers, neurasthenic symptoms, loss of weight, and in the presence of a fresh attack of endocarditis or bronchitis, a temperature of 101° F. (38.33° C.) or over. Whenever valvular disease is the cause, careful auscultation with the patient lying on his back (and this should be the method of choice in examining any cardiac patient) will sooner or later reveal a systolic murmur. It may not be present on the first examination, but it will be evident in a day or two. Here, at times, only the examination of the sputa will settle the question. A history of previous rheumatic fever speaks for valvular disease. Rheumatic fever

is very uncommon in patients suffering from tuberculosis. It may be argued that a mitral regurgitant murmur may coëxist with pulmonary tuberculosis. It is true that this is possible but it is the exception and not the rule, and in the presence of a mitral cardiac murmur without any distinctive and positive evidences of tuberculosis, one is justified in considering the endocarditis as the most likely cause of the symptoms. The presence of hemorrhage adds a confusing element, but the hemorrhage of cardiac disease is usually a single cycle one, that is, the blood is brought up following some exertion and does not recur, whereas in tuberculosis blood-stained sputa are usually present for several days following the initial hemoptysis. A slight rise in temperature within a few days after the hemorrhage is the rule in tuberculosis. Also, the minor symptoms, such as loss of appetite and digestive complaints, are also commonly aggravated after the hemorrhage, whereas in heart disease the patient generally feels better after the hemorrhage.

Finally, in every case in which there is the slightest doubt the sputa should be examined. Fluoroscopy is sometimes of confirmatory value. The heart of mitral disease shows some enlargement, whereas the typical heart of tuberculosis is characterized by extreme smallness and by its lying in the vertical position; in fact, some röntgenographers assume the diagnosis of tuberculosis on the presence of a few signs and on the small heart alone.

The neurasthenic syndrome so often present in cardiac disease suggests an ordinary nerve exhaustion or *neurasthenia*, and this is a frequent error. The knowledge that there is always a cause for neurasthenia and that chronic endocarditis is a frequent cause of this group of symptoms should be sufficient to prevent the error.

When a systolic *murmur* is heard over the mitral area the question at once arises as to whether it is due to disease of the valves, or to some temporary cause (functional) or whether it is accidental, due to adhesions, etc.

Inspection and palpation are good guides in estimating whether or not the systolic murmur is an organic murmur. If the apex-beat is outside of its normal location and very powerful, then certainly an organic lesion is present. On the other hand, an organic lesion may be present without a marked dislocation of the apex-beat. In addition to organic valvular disease the murmur may be due to dilatation of the left ventricle without organic changes in the valve, being secondary to (1) aortic disease, (2) increased blood-pressure in chronic nephritis, arteriosclerosis, myocarditis and pericarditis, (3) over-exertion, acute fevers, acute nephritis, cachexia.

Indications of organic disease are the following:

(1) The loudness or roughness of the murmur. It is very seldom that a rough, loud, systolic murmur in this location is due to anything else than an organic change in the valve. The following exception to this rule should be noted: the systolic murmur, so commonly heard at the base and apex of the patients suffering from a general arterio-

sclerosis, is usually due to an arteriosclerotic process in the aorta or at the aortic orifice and is transmitted to the apex of decompensation. It is true that such a murmur is often associated with symptoms, but autopsy commonly fails to reveal organic mitral changes.

(2) Enlargement of the heart as evidenced by a displaced apex-beat and increase in the area of cardiac dulness.

(3) A history of rheumatic fever or of chorea.

(4) Age of the patient. In children, except when found in acute fever, it is most likely to be due to previous rheumatic fever. The absence of fever will rule out the murmur due to the other infection.

Indications of mitral regurgitation due to functional dilatation of the left ventricle are the following:

(1) Age of the patient. Myocarditis is not commonly developed before middle life.

(2) Presence of other evidences of arteriosclerosis or of chronic nephritis.

(3) Presence of a non-rheumatic aortic obstruction or regurgitation with hypertrophy and dilatation of the left ventricle.

(4) Dyspnea on exertion without any apparent cardiac lesion. This is likely to be due to myocarditis. Furthermore, the dilatation of the left ventricle may, in rare cases, be due to adherent pericardium, and the systolic murmur heard may also be due to anemia, or to cachexia. In the latter instances it is localized in the mitral area and is not conducted to the axilla or back, and there is no cardiac enlargement.

Furthermore, there is in addition a systolic murmur over the pulmonary area and also a venous hum in the neck. Such murmurs are quite frequent in the fevers of small children.

In general, in children a murmur should not be considered of organic significance when it occurs in non-rheumatic fevers, unless it is very loud and very distinct.

The murmur of mitral regurgitation is seldom mistaken for that of any other organic cardiac murmur, because it is distinctive and usually localized at the apex. It is true that some observers claim to have occasionally heard it better at the base of the heart, but the mass of critical observation is against these findings. When the murmur is due to a relative insufficiency, it disappears under rest and digitalis as soon as the temporary overstrain or dilatation is recovered from, whereas, if the murmur is due to changes in the valves themselves due to organic disease, the murmur will increase in intensity when the muscle regains its strength.

The cardiorespiratory murmurs give most trouble in differentiation, and yet they are comparatively easy to rule out if one continually thinks of the possibility of such a murmur. They are frequently found at the apex, and their chief characteristic is that they vary with the respiratory cycle. They are usually louder during inspiration, and they are usually lost at the apex when the patient holds his breath; on the other hand,

they may only be present under just such circumstances. They undergo alterations with the changes in the position of the patient. Of course this is also true of organic murmurs, but the cardiorespiratory murmurs give one the impression of being nearer to the ear than endocardial murmurs do. The murmur commences suddenly and ends suddenly. It is not conducted in the direction of the axilla, but extends along the lower portion of the chest between the apex and the sternum. A congenital systolic bruit is sometimes a stumbling-block in the diagnosis of cardiac disease, particularly in children. It usually occurs in connection with a normal apex-beat and dulness which extends up as far as the second rib and to the right of the sternum. Because of the thinness of the chest-wall in these children this dulness is very striking when it is looked for, and is of much value in the diagnosis of the congenital lesion. In rare cases a patent ductus arteriosus or an acute pericarditis may produce a murmur that is puzzling, but its nearness to the ear, and the to and fro character of the murmur, are sufficient to rule out endocardial disease. It must be remembered that in the cases of pericarditis an endocarditis is also frequently present. A loud systolic murmur of tricuspid insufficiency due to primary mitral stenosis may be confusing, but here the murmur is never as clear over the mitral region as over the tricuspid area; furthermore, the presence of liver pulsation and a throbbing jugular vein, with other evidences of tricuspid insufficiency, will usually decide. Of course the combination of mitral stenosis and mitral regurgitation is almost the rule in such cases.

Prognosis.—The favorable cases are such as have existed for some years without any of the symptoms of heart-failure.

The eventual outlook is better in mitral regurgitation than in any other lesion. Such a large proportion of these cases are due to relative insufficiency that practically complete recovery frequently takes place.

In the average organic cases at least half a dozen breaks in compensation usually occur before the serious stage of the disease appears. Frequently the intervals between such breaks in compensation may last for months and even years, so that patients frequently live for ten or twenty years after having had what seemed to be a fatal illness with general anasarca, dyspnea, etc.

In no condition in life is the patient so frequently brought to the brink of death without actually succumbing as in mitral regurgitation.

Dyspnea on exercise is the best index of the extent of the lesion. If strenuous exercise can be indulged in without any evidence of dyspnea, there is no reason for regarding the lesion with any immediate concern. The outlook in any case is in exact proportion to the reaction from exercise. Patients regularly recover from early attacks of dyspnea. However, when dyspnea occurs in a patient who has already been in bed for several days the outlook is extremely grave.

As compared with the muscular damage done by the agent causing the valve lesion—whether it is rheumatic fever, arteriosclerosis or lues

—the valve lesion itself is of relatively slight importance from a prognostic standpoint, and there is a strong probability that a mitral murmur present in acute rheumatic fever, and not very marked, will, in one-third of the cases, disappear within six months. On the other hand, a murmur which has lasted for a year will not disappear. The murmur following chorea disappears in about one-half of the cases.

In the case of mitral regurgitation due to rheumatic fever the outlook is better than that due to any other disease.

When syphilis is a cause—and this is not frequent in mitral regurgitation—some permanent improvement may occur under treatment, provided the lesion is recognized sufficiently early, before extensive damage has been done. But on the whole satisfactory medication is disappointing if one expects the same results that are to be obtained in syphilitic lesions of the skin and of other parts of the body.

Whenever there is a high blood-pressure with regurgitation and loss of compensation, the dilatation becomes a serious matter. The already damaged heart-muscle, in addition to its ordinary work, must overcome the peripheral resistance thus added. This soon results in a further break in compensation, so that in mitral regurgitation plus high blood-pressure, once there is a loss in compensation the outlook is gloomy.

If this high blood-pressure can be controlled by change in habits, food, etc., of course the outlook is correspondingly brighter, so that when this combination is found, one should be careful in giving an unfavorable prognosis at the first examination.

A very great fall in blood-pressure is of serious import. This is true even if the blood-pressure has been quite high, say 180 or over, at some time. The association of organic mitral regurgitation with a kidney lesion, especially if marked dyspnea is present, is an extremely grave combination.

The accentuation of the second pulmonic sound is the surest way of estimating the degree of back-pressure in the pulmonary circuit and is therefore an index of the condition of the left side of the heart. This powerful accentuation may go on for years provided no intercurrent infection takes place, and the patient may not be any worse than when first seen.

This accentuation is usually accompanied by some dyspnea on exercise. A good, full pulse without atheroma is a favorable sign, because it usually indicates a good heart-muscle.

Murmur.—No matter what the character of the murmur may be, with the apex in a normal position or nearly so, there is no immediate danger. Likewise, a persistence of the first sound indicates that there is no likelihood of immediate termination. In advanced cases the murmur takes the place of the first sound, and this makes the outlook worse. In general a loud murmur offers a better outlook than a faint, weak murmur. The murmur with the worst prognosis is a short whiff, changing in strength and duration with each beat.

There is no physical sign so terrifying to the young practitioner as the irregularity of the pulse of auricular fibrillation. It is positive proof of a bad muscle, yet many such patients do live with this irregular pulse for a decade, with little or no distress, and as far as one can ascertain either from a study of the sounds or of the tracings, there is no way of stating when any serious consequences will follow. Of course this does not mean that it is not a serious lesion. It is always associated with muscular and usually with valvular changes which render the heart far from normal. But if the lesion has existed for some months without any apparent ill effect as such, then one cannot consider that the altered rhythm offers us any basis for an immediate prognosis, although we do know that eventually decompensation is almost certain to follow.

Treatment is also more satisfactory in this particular lesion than in any other.

The common irregularity associated with extra systole must not be mistaken for auricular fibrillation. Ordinarily in sound hearts this extra systole has no evil prognostic meaning. When it occurs for the first time in the course of mitral diseases it may not be dismissed so readily. Auricular extrasystoles are often the forerunner of auricular fibrillation, and without instrumental means it is impossible to distinguish them from the relatively harmless ventricular variety. The extrasystole due to digitalis toxemia must always be kept in mind.

There are some differences between the prognosis of mitral regurgitation in children and that in adults. It is fair to assume that a lesion causing much deformity of the valve in a child has a serious prognosis. As a normal heart enlarges, the cavities of the heart must correspondingly enlarge and the valve must enlarge and lengthen from the base to the free edge. The deformed and sclerosed valve can scarcely be expected to do this, and the separation between the valve edges must grow correspondingly greater, forming an increased regurgitation as the heart grows older. After the first signs of broken compensation in children, the downward progress is more rapid as a rule, inasmuch as the adult has noticed minor symptoms much earlier than the child and has taken better care of himself.

Among these early signs in children that are frequently overlooked is a *loss of mental power* and of emotional control. The child is irritable and does not get on well at school; but the first symptoms to attract attention are usually the major symptoms, dyspnea, dropsy and hemorrhage.

With the failure of compensation there is rapid loss of weight, and appetite, and other distinctive symptoms.

The ease with which intercurrent infections set up acute endocarditis renders the prognosis always less favorable in children. This is the lesion most commonly met with in children, and the younger the child the worse the outlook.

If there has been a marked break in compensation before puberty, adult life is rarely attained, many of the patients dying in consequence

of an acute endocarditis. On the other hand children who have not had fresh attacks of rheumatic fever and frequent head colds very generally go on through life with little or no distress except palpitation and dyspnea on severe exertion. So in the absence of evidences of broken compensation one is justified in giving a fairly favorable prognosis as to the outlook in cases of mitral regurgitations in early childhood.

Mitral regurgitation *as such* seldom kills. Usually stenosis is added before the fatal issue is imminent. This combination becomes evident from:

- (1) The increased loudness of the systolic murmurs, with strong apex beat.
- (2) Accentuation of the second pulmonic sound at the apex.
- (3) Reduplication of the second sound.
- (4) A murmur with the second part of the reduplication.

When this group is persistent, mitral stenosis has been added and the outlook is growing darker.

Mode of Death.—The sufferer from mitral disease nearly always dies eventually from the complications, particularly those in the lungs, such as bronchitis or pneumonia, sometimes from diarrhea due to croupous enteritis. These patients usually die in bed. Cold weather is particularly fatal to them, even though they are not exposed to it. Sudden death in cardiac patients who are exposed to the cold during a cold wave is by no means uncommon. A prolonged hot spell is apt to be the final cause of death in a cardiac patient who is ill in bed during the summer. This is particularly true if there is much humidity. A fair proportion of these patients die at stool, possibly because of the exertion. The presence of marked mental symptoms, particularly delirium and hallucinations, in mitral diseases, are among the most certain signs of approaching death. An up and down movement of the abdomen exactly opposite in time to that of the chest in inspiration and expiration in a manifestly ill cardiac patient generally indicates approaching death. The patient seldom recovers from stupor and coma in mitral disease, but death in coma is not relatively common in these patients. Persistent vomiting, diarrhea or dysentery are usually grave symptoms in a cardiac patient with broken compensation. Rapid breathing, following a Cheyne-Stokes respiration, is generally an indication of a fatal termination. Long apneic intervals in the Cheyne-Stokes phenomenon are also of bad omen. The fact that a patient who has suffered from a long period of dyspnea is suddenly able to lie down flat and sleep, in the absence of any other improvement, is generally a sign of approaching death. A low-lying heart flat on the diaphragm, as shown by x-ray, is found in the type of patient who is apt to die suddenly. Sudden death without any warning is an extremely rare event in mitral regurgitation, except when arteriosclerosis is the cause of the lesion.

Pathology.—**PATHOLOGICAL PHYSIOLOGY.**—The changes found post-mortem are sclerotic, ulcerative, or vegetative alterations of the cusps

or often of the chordæ tendinæ. Often there is infiltration or shortening of these structures. The most common evidence of relative insufficiency is a uniform thickening of the free valvular margin with some contraction.

In the early stages the left auricle is hypertrophied; in the latter stage it is dilated and atrophied. The auricular surface of the anterior cusp usually shows the most marked changes.

The early microscopical evidence of rheumatic endocarditis consists of small nodules on the edges of the cusp. When changes occur later they are for the most part due to involvement of the chordæ tendinæ, which are thickened or shortened. Thus rheumatic disease of the mitral valve is in its serious aspects a disease of the chordæ tendinæ. The mitral valves fail to prevent leakage, either because of organic changes or because of failure of tonicity of the auricular muscular sphincter (functional). This lack of tonicity on the part of the sphincter may be due to degeneration of the muscle or to pure weakness.

Any great enlargement of the ventricle with the consequent shortening of the papillary muscles must permit of some regurgitation. The leaks occurring at the mitral valve as a result of muscular weakness are due, in one group of mild cases, to weakness of the papillary muscles, which allow the valve to be slightly elevated, thus permitting a small stream of blood to pass by it; or, because of the great dilatation of the left ventricle, the mitral orifice becomes larger and wider than the area of valve surface, so that considerable leakage occurs.

This functional insufficiency occurs in toxemia, overstrain, anemia, and, in the case of convalescents, from acute disease. It is the added functional lesion, or, to be more exact, the result of muscular insufficiency, which is finally responsible for the breakdown in most valve lesions. It is the exception for valve changes in themselves to be responsible for the loss of compensation.

When the condition is due to vegetations, they prevent coöperation of the valves and permit the blood to regurgitate.

The part that functional insufficiency plays in cardiac pathology is evident in the rapid recovery under rest in most cases of cardiac failure, even though the organic lesions remain the same. This functional regurgitation explains why a case presenting all of the evidences of mitral regurgitation during life may yet show no organic change postmortem. In a majority of the cases of organic regurgitation there is an added obstruction or stenosis.

MITRAL STENOSIS

Etiology.—There is a growing feeling among cardiologists the world over that mitral stenosis is the serious mitral lesion, and that mitral regurgitation, when it becomes immediately serious, is so because of an added mitral stenosis. Therefore, much of the description of the

symptomatology of mitral stenosis is applicable to mitral regurgitation as well. The lesion is much more common in women than in men.

Probably 75 per cent. of all the cases met with in early life are due to a previous *rheumatic fever*. *Chorea* is the next most frequent cause. After this, *tonsillitis*, and, later in life, *arteriosclerosis* and *syphilis*, follow in order of frequency. There is no doubt that even in primary cases associated with rheumatic fever there are two types of cases. In the endocarditis which usually accompanies well-defined rheumatic fever, the area involved by the inflammation is considerable. The whole inside of the auricle and ventricle, and usually the muscle as well, are to some extent infiltrated with small areas of round-cell inflammation. As a result of this contraction following this, of course, there is shortening of the chordæ tendineæ and retraction of the mitral leaflets, so that there is constriction and regurgitation. This is the common type. When inflammation is more limited and involves the mitral ring on its auricular aspect, the process is slower and the whole course of the disease less striking. In this type we are apt to find occasional pains in the joints or muscles, but no well-defined attack of rheumatic fever. It is in these cases that one most frequently finds the classical picture of mitral stenosis. Many of the patients think so lightly of their pains and aches that they deny ever having had rheumatic fever.

The type of mitral stenosis met with in Russian emigrants, particularly among women, deserves particular attention, as it is becoming a frequent clinical entity in this country. In many respects the history resembles that of the second class of cases mentioned above. There is this exception, however, that the disease, once the symptoms become noted, appears to progress more rapidly than is usually the case with those following rheumatic fever.

Symptomatology.—CLINICAL HISTORY.—The subject suffering from mitral stenosis presents one of two more or less distinct clinical pictures. Either the condition is a primary affection, or it is associated with or secondary to mitral regurgitation. In the latter instance the picture is usually dominated by that of the accompanying regurgitant lesion.

In the primary cases, certain types of patients predominate. Why this is so it is difficult to explain. The patient is seldom very tall or large. The women are, however, often quite stout and florid. There is a yellowish pallor of the forehead and around the nose and mouth. This is frequently accentuated by the presence of red cheeks. As the disease advances, this congestion acquires a purplish hue which enables one at times to make a guess at a glance as to the lesion present. In children, the subjects of mitral stenosis following attacks of rheumatic fever, there is often a failure of development. They are sickly, pale and anemic, and cannot compete with other children because of the shortness of breath that is present. They are subject to frequent attacks of bronchitis, and seldom live to be more than thirty years of age. In these primary cases the patient goes on for years with few

symptoms, and even these are taken as a matter of course. Shortness of breath, or palpitation on unusual exertion, or sticking pains over the heart and a choking sensation in the throat, are accounted as the portion or lot of the female sex, among whom the disease is most common. These symptoms are much more marked at the menstrual period, but are rarely of sufficient severity to require medical aid. Furthermore, these patients are naturally optimistic and seldom complain of their distress, which they have come to count as a part and portion of their existence. As years go on dyspnea is induced by less and less effort. A short single effort cough is generally present, and is particularly noticeable when the patient is climbing stairs or during any physical or mental exertion, such as beginning a conversation, etc. Nose-bleed and hemoptysis on mental or physical exertion are not uncommon. Such patients are particularly susceptible to attacks of bronchitis during the winter months; acute infections, as well as fresh attacks of endocarditis, associated with head colds, pharyngitis, etc., are very common. These attacks are usually associated with increased temperature (from 100° F. to 102° F., or 37.77° to 38.88° C.), and persist for from one to two weeks. They are nearly always accompanied by an aggravation of the symptoms previously complained of, and bring about a temporary loss of compensation, sometimes so severe as to threaten life. Recovery usually ensues, and for a period of months, and even years, the patient is apparently as well as ever, except that the dyspnea is more easily induced than it was formerly. Pains in the chest resembling angina pectoris are occasionally complained of following severe exertion. Recovery from such attacks, in those whose disease is of rheumatic origin, may be generally prophesied. When there is a complete failure in compensation, the symptoms are largely those described under Mitral Regurgitation. The condition is first evidenced by signs of stasis in the lungs. The attacks of shortness of breath become more frequent, and later on are more or less continuous. At first these dyspneic attacks, which occur independently or on exertion, are present only during the night from twelve to four o'clock; later they appear during the day as well. Sleep is impossible, except for short naps. Cheyne-Stokes breathing is a frequent accompaniment, especially in those past middle life. Sooner or later most of the other symptoms of broken compensation associated with mitral regurgitation and tricuspid regurgitation appear. General dropsy and venous engorgement, although early symptoms in mitral regurgitation, are comparatively late symptoms in mitral stenosis. Marked enlargement of the liver, and ascites, are the rule in advanced cases. Ascites occurs more early in the broken compensation of mitral stenosis than in that of mitral regurgitation. Cough is present at intervals throughout the course of the disease. The sputum is frequently reddish in color. It must be distinguished from the bloody expectoration of the attacks of hemoptysis, which are described elsewhere. This red color is due to hemosiderin, a yellowish-brown pigment contained in large nucleated cells, the so-called heart-failure cells.

These are the results of brown induration of the lungs consequent on the long-continued back-pressure in the lung. These cells occur in other forms of endocarditis, but they are more common in old mitral stenotic lesions than in any other pathologic condition. The occasional accompaniment of paralysis of the recurrent laryngeal nerve, as described under Pathology, should be kept in mind as a possible cause of the hoarseness and loss of voice. Auricular fibrillation is more common in mitral stenosis than with any other lesion, and develops sooner or later in the majority of cases during the course of this disease. Attacks of paroxysmal tachycardia sometimes take the place of auricular fibrillation.

PHYSICAL FINDINGS.—Inspection.—The facies is sometimes suggestive. Pulsation is usually prominent over the region of the apex-beat. It may also be evident near the sternum in the second and third left interspace. When compensation is broken it is visible in the epigastrium.

Such pulsations are much more common in childhood because the chest-wall is more pliable. A convenient way of demonstrating this is by sticking small pieces of paper or cardboard that have been folded at right angles to resemble the letter L perpendicularly over the apex and base of the heart. In this manner it can be easily shown that both of these regions do not raise the paper at the same time. The lower one moves with the ventricle while the movement of the other corresponds to that of the auricle. Sometimes retraction of the third, fourth and fifth interspaces may be seen corresponding to each systole. Bulging of the chest-wall close to the sternum and in the epigastrium is occasionally quite marked in children. Should pulsation be present over this area and absent at the nipple, the fact indicates hypertrophy of the right ventricle. In these cases this is the chief impulse, and it is more marked than over the left ventricle. If adherent pericarditis can be ruled out, Hare thinks that there is strong evidence in support of the causal rôle of mitral stenosis in the production of this pathology.

Palpation.—On palpation a pulsation is felt corresponding to the apex-beat; this is usually strong, sudden, short or tapping. Also, in thin chests, a pulsation may be felt near the sternum in the second and third left interspaces. The *thrill* is one of the most valuable points in diagnosis. It is presystolic in time and is best felt in the fourth or fifth interspace near the line of the nipple. The thrill stops suddenly on systole. If aortic regurgitation can be excluded, the diagnosis of mitral stenosis may be made on this basis alone. The thrill varies in the same patient, being present at one time and absent a few hours later. Exercise and change of posture will often serve to elicit it. When the thrill is not felt in either the erect or the horizontal position, the patient should be turned over on his stomach and the apex palpated. The thrill is usually most marked during expiration. It frequently disappears when there are marked evidences of dilatation. The heaving impulse near the line of costal cartilages on the left side, not

palpable at the nipple, is a counterpart of the signs mentioned above under Inspection. The cardiac impulse itself frequently gives one the sensation as if a jet of liquid were projected against the hand. Pulsation of the edge of the liver is due to back-pressure from the tricuspid regurgitation, a common consequent of mitral stenosis. One must not mistake the impulse transmitted from a dilated heart.

Percussion.—Early in the disease there is very little evidence of enlargement beyond the right border of the sternum; when this occurs it is the first evidence obtainable on percussion. When dulness is present on the left side it is quite high up. Later on in the course of the disease the dulness is of course increased to the left and beyond the nipple, and may extend as high as the third rib. This dulness is largely due to cardiac dilatation, secondary to the stenosis. It corresponds to a short wide oval and may be verified by *x-ray* examination.

Auscultation.—The murmur is the most characteristic physical sign. This begins during the diastole. It gradually increases while the auricle contracts, and becomes most noticeable just before systole; hence it is called presystolic. The sound of the murmur is *crescendo* in character, and for purposes of instruction may be so described, but the electrocardiogram shows that this *crescendo* quality is due to its proximity to the loud, slapping first sound. Generally the murmur can only be heard in a restricted area. It is usually on a line drawn along the fifth rib from the sternum to the nipple. Sometimes this area is not more than an inch in diameter. On other occasions it may be heard all over the heart, but in general its audibility is the least extensive of all murmurs. It is commonly a harsh vibrating murmur or a thunder-like rumble. The time of the murmur changes from presystolic to mid-diastolic, or even to early diastolic, depending upon conditions within the heart. When compensation is well established it is presystolic; when compensation is broken it is often diastolic. As cicatrization goes on the murmur changes. Even before the murmur is appreciated by the ear a presystolic thrill may be felt. As has been stated with regard to the thrill the murmur changes frequently. If the damage to the valve is recent the murmur is more likely to change. The older it is the more constant. When compensation occurs it often becomes diastolic again, and as the disease progresses one hears the murmur beginning just at the end of the second sound, and often filling the entire interval. It is important to recognize the fact that this murmur is frequently diastolic instead of presystolic, inasmuch as it is so commonly mistaken for the murmur of aortic regurgitation. This is particularly true when the sounds are quite loud and transmitted for a considerable distance away from the usual area. When in doubt as to the timing of the murmur, the examiner should palpate the apex-beat for the systolic shock. It will thus be easy to follow the murmur up to the shock. Sometimes presystolic and diastolic murmurs are heard in the same case, but usually the presystolic murmur disappears on the appearance of the diastolic. Often both disappear on the occurrence

of dilatation, and a systolic murmur alone is audible. The diastolic murmurs of mitral stenosis do not have the rasping character of the presystolic, but are soft or blowing in type. There is a growing feeling that the murmur is always present during diastole, and its audibility, during presystole in one case, and in diastole in another, depends upon modifying circumstances. The diastolic murmurs are best heard near the sternum along the fourth rib, whereas the *crescendo* has its home near the nipple. This is particularly so in children. It is also very noticeable in gallop rhythm that the murmur is always tagged on to the third sound near the sternum. To recapitulate, we may put in order of frequency, a presystolic, a mid-diastolic, or a mid-diastolic and presystolic, or a diastolic murmur occupying the whole of the ventricular diastole. Sometimes the murmur can only be elicited by having the patient lie on his abdomen and auscultating while he is in this posture. The murmur of mitral stenosis is often accompanied by a mitral systolic murmur, inasmuch as regurgitation frequently occurs through the narrow rigid orifice. The inhalation of amyl nitrite occasionally makes the stenotic murmur audible. A Bell stethoscope is sometimes better than the usual Bowles type, now in common use. The murmur is often best heard with the patient in the prone position.

The second sign of value on auscultation is the accentuation of the pulmonary second sound. This is best heard at the third interspace on the left side. It is caused by the high blood-pressure in the pulmonary artery, which is produced by the back-pressure of the blood in the lungs. Instead of this accentuation, one frequently hears a reduplication of the second sound. It is best heard at the base, although in a strongly acting heart it may also be audible at the apex. It is due to the failure of the aortic and pulmonary valves to close synchronously. It is produced as follows: When the pressure in a pulmonary circulation is proportionately much above normal the pulmonary semilunar valve closes before the aortic; then the first sound of the reduplication is due to the closure of the pulmonary valve, while the second portion of the reduplication is due to closure of the aortic valve. This is not pathognomonic of mitral stenosis, as it occurs in other conditions. It is present in about 65 per cent. of the cases of mitral stenosis. At the end of the second part of the reduplication, one often hears a murmur. This murmur often lasts throughout the whole of the diastole and cannot be distinguished from the presystolic murmur if it is still present. These sounds may be imitated by the phrase "la-rup-de-de." The "la" corresponds to the presystolic murmur, "rup" to the sharp snapping first sound, "de-de" to the reduplication, in which reduplication the second sound "de" is somewhat longer and often terminates in a murmur. This third sound is sometimes spoken of as the third sound of the heart. The signs thus far enumerated are present either alone or together in a classical case, and the diagnosis may be made on the basis of almost any one of them, certainly when any two are present. However, the diagnosis, especially in early cases, is not always

so easily made. There are several other signs which are of considerable value in directing one's attention to the presence of a possible mitral stenosis. The chief among these is a slapping first sound heard at the apex. This is often the only phenomenon to call attention to the possibility of mitral stenosis. This first sound is so entirely different from that of any other condition that it attracts attention at once. It is only in neurasthenia that one meets with such a forcible beat, and then other points such as the lack of accentuation of the second sound, are sufficient to rule out such a condition. This phenomenon is not present in all cases of mitral stenosis, but it is present in a large percentage of cases and it remains even after the onset of broken compensation. It is lacking usually if much regurgitation is present. It is only heard over a small area about the apex. Another evidence that mitral stenosis is probable is the presence of auricular fibrillation, for this is the disease *par excellence* wherein one finds this irregularity. Usually when auricular fibrillation develops the presystolic murmur disappears. The reason for this is that in fibrillation the auricle is nothing more than the continuation of the vena cava. There is no effort to contract in this part of the heart, so that no propelling force is exercised in forcing the blood through the narrow orifice and thus producing murmur. There is another diastolic murmur which is frequently heard as a secondary murmur in mitral stenosis. It is best heard in the left third and fourth interspaces along the left border of the sternum. By some clinicians it is interpreted as being due to a relative insufficiency of the pulmonary valves due to the high pressure in the pulmonary artery and dilatation of the right ventricle. It was described by Graham Steele, and is known as the Graham Steele murmur.

Pulse.—In the past there has been a wide divergence in the description of the pulse of mitral stenosis, one group of observers stating that it is a small full pulse occurring between beats, and that it is characterized by moderately high tension, so that it can be rolled under the finger between the beats. Others contend that it is small, soft, and characterized by lower tension (mitral pulse). As a matter of fact either of these conditions may be present in mitral stenosis.

Recent observations show that rheumatic fever affects the kidneys as well as the heart, in a large percentage of cases, and this would explain the pulse as described in the first group, whereas in the second group there is no organic involvement of the kidney.

The development of auricular fibrillation can often be traced from the beginning of irregularity. There is commonly an inequality in the force of the beats without any decided change in the rhythm. Thus some of the beats fail to reach the wrist, but the rhythm is still constant, so that the heart-beats may be regular and yet the pulse at the wrist irregular. Later the irregularity in rhythm becomes marked over the heart as well, as auricular fibrillation becomes established.

SPECIAL FINDINGS.—Blood-pressure.—There is no characteristic change in blood-pressure. The pulse-pressure is frequently diminished.

Pulse-tracing.—There is no pulse-tracing which is characteristic of the disease. However, when fibrillation appears, as it does so frequently in mitral stenosis, the tracing is quite characteristic.

Electrocardiogram.—In some cases of mitral stenosis the enlargement of the P-wave is an indication of auricular hypertrophy. Such waves are often one-fifth instead of one-tenth as high as the R-wave. They are often prolonged and have a bifurcated or flattened summit.

The hypertrophy of the right ventricle which accompanies such cases is indicated by the direction of the leads of the electrocardiogram. Normally the R-wave is directed upward in 3 leads, whereas in mitral stenosis R 1 is directed downward, while the R-wave of lead 2 is smaller than that of lead 3. This fact is of some value in differentiating those cases of mitral stenosis in which diastolic and presystolic murmurs are present, due to aortic regurgitation with an Austin Flint murmur.

X-ray Findings.—Early in the case orthodiagrams show a relatively small oval with a vertical axis; the enlargement of the left auricle may be evident in the picture, and later on in the disease the addition of mitral regurgitation produces a picture indistinguishable from that of the latter disease alone.

Diagnosis.—**PHYSICAL SIGNS.**—In simple, uncomplicated primary mitral stenosis there is as a rule little difficulty in making a diagnosis. The characteristic *crescendo* murmur, once well fixed in the mind, is seldom forgotten. With the thrill and marked accentuation or reduplication of the pulmonic second sound there is sufficient evidence upon which to base a diagnosis, and where there is any doubt, the presence of the slapping first sound easily clinches it. But all cases of mitral stenosis do not present the presystolic murmur nor the other characteristics; on the contrary, the murmur is often diastolic in time and may be heard over a more extended area than that over which the murmur of mitral stenosis is usually distributed. The other distinguishing findings may be in abeyance on the day of examination. For that reason, of all the common heart lesions mitral stenosis is the one which is most likely to escape detection. The murmur itself is the most uncertain and variable of all the cardiac murmurs. In doubtful cases it is sometimes present and absent on the same day, even changing with the position of the patient. Furthermore, it is frequently accompanied by the murmur of regurgitation, and the latter may be so loud that it obscures the murmur of stenosis.

In general there are five other conditions producing a diastolic murmur over the heart, and while the tone of each is usually different, the extent of transmission is sometimes such that the practitioner is in doubt as to which category the murmur belongs. These murmurs are:

(1) That of aortic regurgitation, usually best heard at the second right intercostal space or at the midsternum opposite the third costal cartilage and well transmitted down along the right or left border of the sternum.

(2) The Graham Steele murmur, best heard over the left third and fourth interspaces near the sternum and not transmitted.

(3) The murmur of pulmonary regurgitation, audible in the same location as the Graham Steele murmur, and in the present state of our knowledge, indistinguishable from it.

(4) Tricuspid stenosis, an extremely rare murmur, best heard on the right side of the sternum out toward the right nipple.

(5) The so-called Austin Flint murmur or diastolic murmur heard at the apex in some cases of advanced aortic regurgitation.

The question which causes most difficulty is the differentiation between the murmur of aortic regurgitation and that of mitral stenosis. This is one of the most difficult diagnostic problems, particularly when the other signs of aortic disease are not in evidence.

The murmur of aortic regurgitation is confined almost entirely to the base of the heart, and is transmitted upward and downward, yet occasionally it is quite distinct over the mitral area and beyond. But its point of maximum intensity is always up near the second costal cartilage, whereas the point of maximum intensity of mitral stenosis is always down in the neighborhood of the apex.

In the diastolic murmur of mitral stenosis a short interval often exists between the second sound and the murmur. This is rarely the case in aortic regurgitation, the murmur being continuous with or taking the place of the second sound. A slapping first sound with enlargement of the right heart with a gallop rhythm and a small pulse commonly indicates the presence of mitral stenosis, even though no murmur is heard.

In aortic regurgitation the apex-beat has a much more prolonged and exaggerated appearance, whereas that of mitral stenosis recedes almost instantly.

A thrill, if present, is of decided value. Yet with the Austin Flint murmur which may accompany aortic regurgitation a thrill is sometimes present, and these are the difficult cases, because it is here that the question arises not so much as to whether one valve disease or the other is present, but as to whether more than one valve is involved. In aortic regurgitation marked hypertrophy is present, whereas in mitral stenosis, if uncomplicated, none is demonstrable either by percussion or by x-ray. When, however, mitral regurgitation is present with mitral stenosis there is considerable hypertrophy, but not nearly as much as in aortic regurgitation.

It may be argued that in the early stage of aortic regurgitation there is little hypertrophy, but in nearly every instance when the patient presents himself for examination marked hypertrophy is present. It is, however, on the basis of signs outside of the heart that one must make the differentiation between these two simple lesions.

A previous history of syphilis or a positive Wassermann will almost clinch the diagnosis in favor of aortic regurgitation; on the other hand, a history of *rheumatic* fever inclines one to decide in favor of mitral

stenosis. Yet it is not very rare to find aortic regurgitation due to rheumatic fever.

In mitral stenosis pulsation of the vessels is not common; in aortic regurgitation it is seldom or never absent. A marked Corrigan pulse is never observed in mitral stenosis. Duroziez's sign and the capillary pulsation of aortic regurgitation is also of decided value in excluding mitral stenosis. A loud systolic snap, the pistol-shot sound, in the large arteries, is often present in aortic regurgitation.

Blood-pressure.—In mitral stenosis there is not more than 50 mm. difference between the pressure in the arm and in the leg, whereas in aortic regurgitation this difference is between 60 and 120.

This rule is of course not universal, because in some cases of mitral stenosis associated with arteriosclerosis a greater difference than 50 may be recorded, but it is nevertheless a good working rule.

Pulse-pressure.—Ordinarily the pulse-pressure in mitral stenosis is a little below normal, whereas in aortic regurgitation it is nearly always double the normal.

Graham Steele Murmur.—In a small proportion of cases of mitral stenosis, one hears, in the third and fourth interspaces, to the left of the sternum, a soft blowing diastolic murmur as described by Graham Steele and named after him. It does not replace the second sound, but follows it after a short interval. It is sometimes heard all along the sternum.

As far as can be determined it is due to dilatation of the right ventricle with consequent functional insufficiency of the pulmonic valves. It is best heard when the patient is lying on his back; sometimes it is not heard when he is in an erect position; or again it may be heard only when he is in this position. It may or may not be affected by either inspiration or expiration. Exercise usually intensifies the murmur, which is best heard at that time. Pressure by the stethoscope sometimes renders it audible. It is not transmitted for more than an inch. Thus we have a secondary diastolic murmur in mitral stenosis just as we have a secondary murmur in aortic regurgitation, in the form of the Austin Flint murmur—two strong names for two weak murmurs.

As has been stated above, the murmur of pulmonary regurgitation is to all intents and purposes similar to and indistinguishable from that of the Graham Steele murmur.

Tricuspid Stenosis.—The murmur of tricuspid stenosis may be either presystolic or diastolic. The character of the murmur is just the same in tricuspid stenosis as it is in mitral stenosis. However, the murmur of tricuspid stenosis is usually heard only over the tricuspid area to the right of the sternum, whereas the murmur of mitral stenosis is commonly confined to the region of the left nipple.

Tricuspid stenosis is usually accompanied by a mitral stenosis. MacKenzie believes that we may make a diagnosis of tricuspid stenosis when pulsation of the liver, as determined by means of the sphygmographic tracing in the cardiogram, is found to be of the auricular type.

The early appearance of marked cyanosis and extensive edema is evidence in favor of the predominance of tricuspid stenosis as compared with mitral stenosis.

Austin Flint Murmur.—The presence of the Austin Flint murmur may raise the question as to whether true mitral stenosis is present in addition to aortic regurgitation or whether we have aortic regurgitation with a functional mitral stenosis due to ventricular dilatation. The Austin Flint murmur is not harsh and vibratory, as is that of mitral stenosis, and if a thrill is present it is not purring in character. In uncomplicated mitral stenosis the apex is in the normal position, whereas when the Austin Flint murmur is present the apex is displaced far to the left because of the enlargement of the left ventricle consequent on the aortic regurgitation.

The Austin Flint murmur is of course heard in the same location as the murmur of mitral stenosis. In fact, the most satisfactory explanation of its origin is that there is a relative functional mitral stenosis, produced by the dilatation of the ventricle, so that, given a diastolic murmur at or about the nipple, the presence or absence of aortic disease and its concomitant symptoms will determine the diagnosis.

The sound due to an adherent pericardium seldom causes trouble in diagnosis. This is particularly true in children. This sound is rather a rumble than a murmur, and is best heard in diastole at the apex. It does not have the same sharply defined localization as does the murmur of mitral stenosis, and the peculiar slapping first sound of mitral stenosis is not present.

Combined Murmurs.—When the question arises as to whether or not one is dealing with combined mitral disease, it may be well to remember that the murmur of aortic disease is frequently transmitted to the apex of the left ventricle and is not so well heard over the body of the right ventricle. In such a case one will hear the systolic or diastolic murmur of aortic disease down to and to the left of the apex, but not to the right of the apex. In such a case the hypertrophy is very much more marked than in ordinary disease; furthermore, the apex-beat is much more thumpy in character, as felt under the hand, and, finally, the diagnosis must frequently be made on the basis of signs outside of the heart, as mentioned above. It is very uncommon that the murmurs of mitral disease are transmitted to the base, but when such is the case the final judgment may again be based on the peripheral signs outside of the heart. When combined lesions of both orifices are present, the murmurs are most clearly heard over the ordinary points of greatest intensity; then they gradually fade as one goes from either apex to base, and gradually increase as apex or base is approached. In solving such problems, one should select one murmur and follow it throughout its course, and then do the same with the others. In the rheumatic cases in children basal and apical involvements are quite common.

In more than one-half of all patients suffering from cardiac disease, a combination of murmurs is present sooner or later.

In the table of F. J. Smith the relative frequency of combinations of murmurs found is given as follows:

A. R. and M. S.....	16.55 per cent.
A. S. and M. S.....	6.12 per cent.
A. R. and M. S.....	5.21 per cent.
A. R., A. S., M. S. and M., presystolic.....	3.77 per cent.

Often these combined murmurs are due rather to relative insufficiency than to true organic change, which is often an effort on the part of nature to prevent serious consequences. For instance, in aortic regurgitation the relative insufficiency of the mitral valve prevents an over-distention.

In advanced mitral disease a marked leakage at the tricuspid valve likewise prevents overdistention of the right heart.

It is only when mitral regurgitation is secondary to aortic stenosis that combinations are apt to be serious in themselves. Aside from this, it is a well-known fact that patients suffering from disease of both mitral and aortic orifices are more prone to develop malignant endocarditis than is the case when either valve alone is affected.

A common difficulty in differentiating murmurs is to determine whether the murmur heard at the base and the one at the apex are due to involvement of one or of both orifices. When the disease at the orifice has persisted for some time, whether it is regurgitation or stenosis, there is nearly always, sooner or later, a concomitant stenosis or regurgitation. If we are dealing primarily with a mitral stenosis which is moderately advanced, there will also be some regurgitation, and the same thing applies with regard to stenosis when regurgitation is the primary lesion. When mitral stenosis and mitral regurgitation are both present there is a possibility of mistaking the seesaw murmur for a prolonged systolic murmur. At another examination, however, we are likely to find a systolic murmur, and the absence of a second sound at the apex justifies the diagnosis of stenosis.

When mitral regurgitation accompanies mitral stenosis, the palpatory signs so marked in uncomplicated stenosis are often not so clear. The presence of the Austin Flint murmur, *i.e.*, a presystolic murmur at the apex present in aortic regurgitation, may be confusing, inasmuch as a thrill is present here as well as in mitral stenosis; but in the Austin Flint murmur there is a strong, long first sound and a much hypertrophied heart, whereas, in mitral stenosis, the first sound is snappy, the heart is not enlarged, and there is an accentuated pulmonic sound.

The individual symptoms are seldom pathognomonic in themselves, because in one instance, a symptom which is usually present to a marked degree in mitral disease may be very pronounced in aortic disease, and *vice versa*; but the ensemble of symptoms is essentially different. Mitral stenosis, in its early stages, commonly manifests itself by lung signs, as dyspnea, cough, and hemorrhage, whereas aortic disease is manifested, in its early stage, by pressure disturbances such

as headache, throbbing, and pain over the heart; dropsy and enlarged liver are, relatively speaking, early signs in failing mitral disease; if they appear at all in aortic disease, it is toward the end. Ordinarily the appearance of either the mitral facies, a history of rheumatic fever, cerebral embolism or fibrillation point to mitral stenosis, rather than to aortic disease.

The presence of hemorrhagic expectoration commonly raises the diagnostic question of the coëxistence of tuberculosis. In fact, mitral disease is more commonly mistaken for tuberculosis than for anything else.

The added presence of a slight rise in temperature due to fresh infection of the valves or to an acute bronchitis, the flushed face, dyspnea, and cough, would seem to make a complete picture of tuberculosis, were it not for the absence of the bacillus of Koch. Yet clinical experience the world over shows that the two diseases are seldom actively present together in the same individual. Every now and then some competent observers come forth with statistics proving that in a series of autopsies the diseases were concurrent, but one or the other of the lesions is always in a quiescent form.

Sears goes so far as to state that 1 per cent. of the cases of mitral stenosis at the Boston City Hospital were presumably tuberculosis; yet close analysis will show that in comparatively few cases could the fatal issue be charged up to a combination of the two active lesions.

If every one is tuberculous, then every patient with cardiac involvement must also be tuberculous, but progressive pulmonary disease in mitral stenosis is the exception. This immunity has been explained on the ground that mitral stenosis promotes pulmonary hyperemia, and it is a well-established fact that hyperemia is the best antagonist against the growth or propagation of the organism of tuberculosis.

In rare cases cardiac thrombosis causes the symptoms as well as many of the physical signs of mitral stenosis. The onset is sudden with great dyspnea, cough, rapid feeble pulse and later, in some instances, a localized gangrene of the foot. The reason for this latter phenomenon is not quite clear. In addition, there is usually a murmur, presystolic in time, and a reduplicative second sound. However, the rapid onset and the previous history are usually sufficient to justify the diagnosis.

Complications and Sequelæ.—In approximately 75 per cent. of the cases of true mitral stenosis there is sooner or later an added regurgitation.

Thrombosis of the left auricle, for reasons to be pointed out under Pathology, is more common than in any other valvular lesion. It cannot be diagnosticated except when the thrombus has been loosened from its bed, and thus furnishes emboli. Embolism of the left mid-cerebral artery is the most common clinical manifestation met with. The consequent right-sided paralysis and speech defect are seldom overcome, and while the condition has a low immediate mortality, it has the worst outlook as to complete recovery of function. If one can exclude syphilis, it is the

most frequent cause of hemiplegia in patients under forty years of age. It may sometimes be diagnosticated by a sudden rapid rise in temperature immediately following a hemiplegia when there is no other explanation for the temperature. Of course the customary rise in temperature which occurs antemortem in most fatal hemiplegias is of no diagnostic value.

Splenic infarcts are probably still more common, but are usually symptomless. Many of the sudden pains complained of by cardiac patients in the lower left side are doubtless due to this same cause, but one cannot be certain of their differentiation.

Pulmonary emboli in cardiac patients arise either from the thrombi occurring in the veins throughout the body or from those arising on the right side of the heart, or more commonly, from clots emanating from the left auricle as mentioned above and reaching the lungs through the greater circulation.

Pulmonary thrombosis is sometimes due to stasis in the pulmonary circulation, thus producing clots in the pulmonary artery.

Infarction, as a result of such obstruction, is fairly common in the latter days of the life of the cardiac patient, but it is neither as dramatic nor as terrifying as when it comes from the left side of the heart.

Pulmonary embolism explains some of the attacks of *hemoptysis*. In others, localized pneumonic areas are responsible for the bleeding. About 20 per cent. of all the cases of mitral stenosis show hemoptysis at some time during their course. It is rarely alarming, and usually the patient feels better after the hemorrhage. Profuse bleeding, however, offers a grave outlook. It often follows emotion or strong effort of any kind. On the other hand, blood-stained mucus is quite commonly expectorated by the majority of patients suffering from dilatation of the right heart due to any cause.

Hemorrhage from the nose is particularly common in children. When it is profuse it greatly depresses the child and hinders recovery. It should be considered a serious complication.

Hemorrhage from the stomach occasionally occurs, and has a greater significance than any other hemorrhagic manifestation.

Hemorrhage from the uterus is not uncommon, but does not seriously affect the patient unless it is very profuse.

Hysterical manifestations are much more common in young women suffering from mitral stenosis than in those suffering from any other valve lesion. They frequently suffer from attacks of dyspnea, palpitation, and even pain closely resembling that in angina pectoris, and much care must be exercised in not laying too much stress on their complaints, thereby causing undue alarm.

The nervous element outweighs the organic, as a rule, and the patient is not in as serious a condition as she appears to be. Such attacks are most common at the menstrual period. Attacks of migraine are also more common than in normal patients.

Auricular fibrillation may be considered a symptom rather than a complication of mitral stenosis, for it is more often present in this form

of valvular disease than in any other. In some instances it begins suddenly and is continuous thereafter; in other cases the irregularity persists for a short time, then disappears and reappears at intervals until it becomes continuous.

In some patients attacks of paroxysmal tachycardia take its place, and this is not to be wondered at, since these two functional disturbances are closely allied, and seem to represent a difference in degree of hyperexcitability rather than a difference in origin.

Venous thrombosis in other parts of the body is more common in mitral stenosis than in the course of any other valvular lesion.

Enlargement of the liver is more common as a consequence of mitral stenosis than following any of the other principal primary cardiac lesions. Ascites likewise arises earlier than in other heart lesions, and persists longer. The reverse is true for mitral regurgitation. Mitral stenosis is often associated with a small kidney. In fact, this association is so common that these conditions appear to have a common infectious origin.

Adherent pericardium is fairly common in children, and some form of pericarditis is present in one-third of all the fatal cases of mitral stenosis.

PREGNANCY.—Mitral stenosis is the most serious valvular lesion associated with a pregnancy. The principal immediate danger is the sudden development of pulmonary edema. However, until there is a decided break in compensation there is comparatively little danger. Many women with compensating mitral stenosis pass through half a dozen pregnancies with no evil effects. If there has been any disturbance in compensation the child is not so likely to live as in normal cases. From 25 to 40 per cent. of such patients have premature labors. As a rule labor itself is well borne, even in uncompensated cases.

Prognosis.—Next to aortic regurgitation, mitral stenosis is the most serious form of valvular lesion. According to Broadbent's statistics, the average age of death is from thirty to thirty-nine years for males and from forty to forty-nine for females. These statistics represent conditions in London, and are not applicable to the cases seen in civil practice in this country.

The reason for the greater seriousness of mitral stenosis as compared with mitral regurgitation, is that the consequences of the obstruction are not so easily overcome.

Mitral stenosis is a disease of youth, and there is more tendency to contraction at that time than later in life; furthermore, the size of the orifice, as a result of the contraction, does not increase, whereas the cavities of the heart will continue to increase as the heart normally grows larger. Thus we find in adult life a normal-sized heart with a mitral orifice the size of that in a child's heart.

Broadbent's four stages form a convenient way of fixing in one's mind the progress of the disease from the standpoint of physical signs as well as of prognosis:

FIRST STAGE.—*Présystolic Murmur.*—Slapping first sound and second sound well heard at the apex, and the accentuation of same over the pulmonic area. The compensation being good, the prognosis is favorable at this time, and the patient is not a source of concern.

SECOND STAGE.—*Présystolic Murmur.*—Thrill and first slapping sound present, but the second almost inaudible at the apex. (Students generally confuse the sounds, and are apt to mistake the first sound for the second.)

THIRD STAGE.—Presystolic murmur and thrill have disappeared, as well as the second sound at the apex. There is a short, sharp first sound. Auricular fibrillation is present. The signs of beginning broken compensation, such as shortness of breath, cough and hemoptysis, are now present. This condition may exist for many years.

FOURTH STAGE.—Broken compensation and stasis; later on signs of tricuspid insufficiency, venous pulse, and pulsation of the liver.

To sum up, as long as the second sound can be heard about the apex there is no immediate danger. When the second is lost at the apex the patient is fairly safe, provided there are no infections, and that the patient does not indulge in excitement or exertion. But there is no reserve force, and the least disturbance is sufficient to induce a break in compensation, so that, to use a slang expression, the patient must constantly "walk the chalk line." This may be impressed upon him better if it is explained that he is like a man walking along the edge of a precipice—he may do so indefinitely, but if the slightest wind strikes him, or the slightest misstep occurs, he will almost certainly fall over; whereas another man (representing one with a sound heart) walking along the same table but several feet from the edge may be struck by the same wind-storm and yet will not fall over the edge. Some such homely expression as this brings his condition vividly to the mind of the patient, and serves to warn better than hours of preaching. Such patients often live a quiet life for many years, but they are in constant danger.

The third group are those with serious symptoms, such as edema, and dyspnea. Here one must judge how severe or how slight the causes are that have brought on the break in compensation.

The reason why women live longer than men is because they usually live a more quiet life. Once a severe break in compensation occurs recovery is not nearly as easy or as frequent as in mitral regurgitation. Among females the greatest single danger lies in pregnancy. No other lesion is so serious to the pregnant woman as mitral stenosis, yet sometimes it has very little effect, some patients going through as many as nineteen pregnancies with no evil results. It is not regarded as seriously as it was in former years. The chief danger is during the fifth and sixth months, and then the calamity generally occurs in the form of acute pulmonary edema. Death from pulmonary edema rarely occurs during labor, but it is usually within two hours after labor that pulmonary edema manifests itself.

If there have been no breaks in compensation, however, previous

to pregnancy, these patients generally do as well as other women who have no such lesion; lactation does not affect them seriously.

When the presystolic murmur disappears and the diastolic takes its place the disease has advanced considerably. Children, of course, have a less favorable outlook than adults. When mitral stenosis is associated with, or due to arteriosclerosis, the outlook is much less favorable than otherwise.

There is a class of patients who present evidence of rheumatic mitral disease without having a history of rheumatic fever. These patients absolutely deny having had articular rheumatism. Generally they give a history of backaches, and of sticking pains in the muscles and in the finger-joints, which they have usually associated with their work.

There is no history of rheumatic fever in childhood, nor any of the severe infectious diseases which are commonly followed by rheumatic fever, yet the heart presents the murmur of mitral stenosis. When there is a break in compensation in these cases they do not do as well as those with a frank rheumatic history. This type is especially common among the Russian Hebrews. The outlook for eventual recovery among those patients is seldom promising.

Of all diseases of the heart, mitral stenosis is most commonly associated with auricular fibrillation. In Carey Coomb's statistics the average age of the onset of this symptom is twenty-six years, and the average expectation of life after that is thirteen years; he believes that most of the cases have their origin in mitral disease before the age of sixteen.

Cerebral embolism is by no means uncommon. The patient rarely recovers completely from the hemiplegia which results, in contradistinction to hemiplegia of cerebral hemorrhage. It is usually a right-sided hemiplegia. Most patients, however, die from gradual heart-failure. There is engorgement of the lungs, bronchitis, edema, pneumonia and death. In estimating the course of heart-failure one must analyse:

1. The course of the symptoms of insufficiency, *i.e.*, pulmonary congestion, dyspnea or exertion, the presence of congestion at the left base, and liver enlargement.
2. The auricular fibrillation. The length of life after this is established varies from five to fifteen years.
3. The failure of the ventricle. When this happens there is intense hyperemia of the lungs. Following this there is frequent hemoptysis. Sometimes this is followed by pronounced relief, but in any case in which it is quite profuse it is a warning of the near approach of death. In such cases, when vomiting becomes persistent, recovery is uncommon. As far as treatment is concerned, the prognosis depends upon how soon the patient is put to bed and given digitalis. When both of these measures are pushed to the limit, *i.e.*, absolute rest, achieved if necessary by the use of opium, and large doses of digitalis, and these measures fail to slow the pulse and lessen the symptoms within ten days, the outlook is very grave.

MODE OF DEATH.—Very often death follows an intercurrent affection. The ordinary patient suffering from progressive mitral stenosis usually dies in bed as a consequence of the progressive edema, anasarca and hydrothorax. Even though the patient is bedridden the end usually comes quite unexpectedly. He is apparently no worse than he has been for days or weeks, or is possibly a little better, when out of a clear sky, during the late hours of the night, an attack of pulmonary edema develops and death closes the scene, or again, the cheerful patient asks for a drink, takes it, thanks the nurse, turns over, and is dead. In this sense sudden death is not uncommon. In the case of those who are up and about and free from marked symptoms, not more than 2 per cent. suffering from this lesion die suddenly.

Pathology and Pathological Physiology.—There are three varieties of the lesion presenting different pictures, depending upon the causes: (1) infectious, (2) arteriosclerotic, (3) congenital.

Of these the first is by far the most common. In addition, one sometimes finds a functional form such as results in the production of the Austin Flint murmur in aortic regurgitation; in this case there is no pathologic change in the mitral valves themselves, but the relative constriction is due to a retroversion of the valves due to the dilatation of the ventricle consequent on aortic regurgitation. However, thus far this is only a theoretical surmise.

There is a rare form due to a congenital lesion; it may also be a result of a fetal endocarditis. This congenital variety is commonly found in association with other congenital defects in patients suffering from hare-lip, cleft palate, etc. Probably a large number of the cases described under this head are due to unrecognized early endocarditis, sometimes becoming manifest between the seventh and fourteenth year of life.

The fact that such patients live longer than those who acquire the disease later on in life may be due to their early recognition of the limitation of activities in the different forms of infection. Hereditary syphilis may be an occasional cause of the infection in these early cases.

A primary lesion and a secondary form are associated with mitral regurgitation. The latter is more common than the former, but because of the accompanying regurgitation it does not produce a definite pathological picture.

Anatomically one meets with four varieties of lesions in mitral stenosis: buttonhole, funnel-shaped, vegetative and, very rarely, cystic.

When the lesion involves the free edges of the valve a funnel-shaped orifice is formed, the mouth of the funnel being situated at the ring, and the small end of the funnel being drawn down toward the apex by the shortening of the chordæ tendinæ and of the papillary muscles, the valve-tissue itself forming the sides of the funnel.

This is the usual type seen early in life, and may be described as the typical infectious type.

Later in life the button-hole variety is more common. This is fre-

quently due to added arteriosclerosis. It is associated with a thickening or shortening of the papillary muscles and chordæ tendineæ. The valve itself does not stretch, as in the early cases, but becomes much thickened, and there is a great increase of fibrous tissue, which leads to puckering of the valves. Often the leaflets unite and form a diaphragm which is perforated by a slit-like opening. This union of the cusps almost entirely closes the orifice and presents the appearance of a button-hole when looked at from above; hence the name. The vegetative form is similar to that described under mitral regurgitation; the cystic form is rare and resembles the vegetative type.

In the heart two forms of thrombi are met with postmortem: One is the infectious type which occurs as the result of endocarditis; these are small, and are generally found on the valve edges. The other form is usually found in decompensating hearts, and is met with in those portions of the heart in which the current of blood is less active and in which there are uneven areas. These conditions are to be found particularly in the appendages of the auricles and to a lesser degree between the columnæ carneæ at the apex of the ventricle. They are much larger than those in the infectious form. Ball thrombi are a special form met with in the left auricle in mitral stenosis.

According to Norris the mitral orifice in men averages 110.37 mm. and in women 92.68 mm. in circumference. The anterior mitral leaflet has a different function from that of the small, fixed, posterior leaflet. The anterior leaflet, in addition to preventing regurgitation in the auricle during the systole of the ventricle, actually forms, together with the septum of the ventricle, a channel which aids in conducting the contents of the ventricle into the aorta, so that the pathology in this cusp is more significant than when it is present in the posterior one.

The earliest effect of mitral stenosis is a hypertrophy of the left auricle; because of the slow output the left auricle becomes extremely full, and forces a large amount of blood into the ventricle. As it continues to distend it finally reaches a point at which dilatation ensues. This dilatation makes itself evident at first in the auricular appendage, because, owing to the unyielding structures with which the auricle is surrounded, there is little chance for this chamber to increase by stretching. Because of this dilatation of the appendix one finds thrombosis in the appendix, either antemortem or postmortem, with great regularity. As a result, this space is a reservoir, as it were, for emboli, and makes for less efficiency in the presence of any strain or infection.

Finally, as a result of venous stasis, the right ventricle hypertrophies and becomes rectangular in shape. After this, dilatation of the ventricle occurs because of the continuous pressure, and tricuspid insufficiency results. Later on this is followed by overdistention of the right auricle. It gradually becomes thinned out, and is nothing more than a funnel-like continuation of the vena cava; thus the functional activity of the auricle is destroyed, and to all intents and purposes it does not

exist. This phenomenon can be demonstrated by the disappearance of the auricular wave in the jugular tracing during auricular fibrillation. While this sequence of events takes place to some degree in all cases, it can never be sufficiently emphasized that it does not take place as long as the muscle of the heart is perfectly sound, or in other words, as long as there is sufficient "rubber" in it to make up for the valve deficiency. It is only when valve and muscle are sufficiently involved by pathological changes that this sequence follows.

As was pointed out earlier, the left auricle can expand only in an upward direction. This expansion upward may result in pressure on the left pulmonary artery, and in that way produce a paralysis of the left recurrent laryngeal nerve by pinching it between the pulmonary artery and the arch of the aorta.

When left ventricular hypertrophy is present it is usually due to other lesions and not to mitral stenosis.

Experimentally, McCallum and others have produced mitral stenosis by introducing a distensible balloon through the auricular appendage and by clamping the auriculoventricular ring. The immediate result of this procedure is the lowering of general arterial pressure throughout the body, and the elevation of pressure in the pulmonary artery, pulmonary veins, and left auricle. The pressure in systemic veins is little elevated. The essential features of this experiment are that the amount of blood in actual circulation is diminished while the rest of the blood stagnates behind the obstruction into the lungs. Such rapid changes, however, do not take place in the hearts of human beings suffering from mitral stenosis.

TRICUSPID REGURGITATION

Etiology.—There are two classes of cases, if one expects the rare congenital cases which are associated with tricuspid stenosis:

1. Those due to a primary lesion of the valve, such as follows acute endocarditis, with resulting fibrosis. This is an extremely uncommon type.

2. Instances of relative incompetence wherein the valves are normal and the dilatation is due, as in mitral regurgitation of the same type, to the dilatation of the right ventricle. In these dilated hearts the normal leaflets are no longer able to close the increased abnormal orifice. This relative incompetence is the most common cardiac lesion and is present in practically all cases of cardiac failure at some time or another. It is always consequent on some other disease. Etiologically it occurs most frequently (1) secondary to valvular diseases of the left side of the heart, particularly the mitral lesions; (2) acute and chronic myocardial involvement, due to infection, toxemia or degeneration; (3) pleuro-pulmonary diseases associated with increased pressure in the pulmonary circulation, as in emphysema, cirrhosis of the lungs and adhesive pleurisy, or (4) the temporary dilatation and over-strain of the right

ventricle, due to any unusual or sudden physical exertion, the "safety-valve action" of Wilkinson King.

Osler calls attention to the fact that one may imitate tricuspid functional incompetency by holding the breath for one minute; as a result of this the right border of the heart extends to the right of the normal at least an inch further than before. This may be determined by deep percussion or by *x-ray* examination.

Symptomatology.—The symptoms have been described under Mitral Regurgitation, which is so commonly the diagnosis in the first instance.

PHYSICAL SIGNS.—*Inspection.*—The face and extremities are cyanotic; the veins show a distinct pulsation. There is also epigastric pulsation. When the disease has developed slowly, or in young people, the precordium is distinctly bulging. The retraction of the third and fourth interspaces between the sternum and parasternal line is quite marked.

Palpation.—When the condition is well advanced, a systolic pulsation is frequently felt over the right ventricle. The apex is diffuse; its location depends upon the primary disease. If mitral regurgitation is present it is usually displaced beyond the nipple line. If early mitral stenosis is the cause, it is within the nipple line.

The liver pulsation, when present, is pathognomonic. To determine this sign the patient should lie with his arms extended above his head, with the palm of the physician's left hand over the right mid-axillary region, and his right hand over the upper abdominal region. An expansible pulsation of the liver, synchronous with the systole of the heart, will be felt, if this disease is present.

In well-advanced cases the venous pulse, instead of being diastolic in time, is systolic, the positive venous pulse of Siegel. This is due to the fact that the auricle, in decompensated hearts, is to all intents and purposes a continuation of the vena cava, so that, when systole of the right ventricle occurs, the blood is forced in two directions: (1) into the pulmonary artery, and (2) up into the vessels of the neck. In the earlier stages of the disease this does not occur. The jugular tracing is quite characteristic, the "ventricular type" of Mackenzie.

Percussion.—Cardiac dullness extends to the right of the sternum and is often as much as two or three inches beyond the midsternal line.

Sometimes the relative tricuspid insufficiency produces a wider area of dullness than does that due to organic lesion, but the percussion findings are more permanent in the organic lesions. The murmur takes the place of the first sound and is heard throughout the whole systolic period. It is a systolic murmur and is best heard on the left side very near the sternum in the fourth and fifth interspaces, or at the base of the ensiform cartilage. Very frequently it is best heard on the right side of the sternum. It is transmitted downward along the sternum, but not to the apex. It gives one the impression of being superficial or near the ear. It is a very fugacious murmur. Sometimes in the course of an examination it is present only during a few beats. It is more marked after exertion and in certain postures of the body.

Hirschfelder suggests that it may be elicited by causing the patient to bend forward at an angle of 45 degrees occasionally. Sometimes it is best heard when the patient's head is lying over the edge of the bed, thus putting the vessels under a tension. The physician then listens over the tricuspid region.

In spite of all these maneuvers, it is frequently very difficult to elicit a murmur, even though one is quite certain that tricuspid regurgitation is present. The murmur is generally faint or absent when there is a large leakage due to severe insufficiency; on the other hand, slight regurgitation generally produces distinct murmurs.

Differential Diagnosis.—The principal difficulty in the diagnosis is differentiating between mitral regurgitation and *tricuspid regurgitation*. The murmur occurs at the same time in both, and the mitral murmur is frequently transmitted over a large area of the heart.

The difference is largely an academic one, because sooner or later, mitral disease is followed by tricuspid regurgitation. In practice, the diagnosis of tricuspid disease is founded upon the presence of symptoms rather than upon physical signs.

In tricuspid disease the murmur is not as rough as the mitral form. It is more superficial and is higher-pitched. The mitral murmur is rarely heard over the right side of the sternum.

In tricuspid disease the pulsations are visible over the right border of the heart, whereas in the mitral regurgitation they are visible to the left.

In differentiating the murmurs it is well to remember that the mitral systolic murmur has its point of maximum intensity somewhere near the nipple and gradually diminishes in intensity as one passes toward the right. On the other hand, the murmur of tricuspid disease has its greatest intensity at the left sternal border, and it also diminishes as one advances to the left, so that there is an area between these two regions in which the sounds are faintly heard. The diagnosis must generally be based, however, upon the presence of the jugular and hepatic pulsation, dropsy and cyanosis.

Sometimes the question arises as to whether the disease is organic or functional. In general the organic murmurs are rough, while those resulting from functional insufficiency are soft and blowing.

In organic insufficiency, after compensation has been reëstablished, the positive venous pulse still remains. In relative insufficiency under the same conditions the positive venous pulse changes, so that the auricular wave again becomes prominent.

Prognosis.—The prognosis depends upon the primary cause. In those cases secondary to mitral stenosis due to relative insufficiency, the immediate outlook in the early attacks of decompensation is favorable. In general the outlook has already been described under Mitral Regurgitation and Mitral Stenosis.

In aortic disease, the presence of tricuspid insufficiency is the beginning of the end. In primary organic disease of the tricuspid orifice the progress is usually steadily downward.

Pathology and Pathological Physiology.—In the organic cases the lesions are the same as those found in mitral disease only, of course, situated in the right heart. When the regurgitation in the cases of relative insufficiency is very marked, the dilatation of the right auricle is the first and most characteristic gross lesion.

In the organic cases both auricle and ventricle are hypertrophied as well, because here the condition has been of longer duration and more gradual in appearance. The chief effect of this is evident upon the systemic veins; the back flow of blood causes the venous pressure to rise (20 mm. of Hg). This causes stasis and is followed by dropsy. In all cases which have existed for a long time, or in which there have been frequent attacks of broken compensation, the congestion in the liver frequently results in the production of "nutmeg liver."

TRICUSPID STENOSIS

Etiology.—This is a comparatively rare lesion. In a total of 12,000 autopsies at Guy's Hospital, covering a period of twenty-six years, only 87 cases were found. Among 24,000 cases admitted to Johns Hopkins Hospital, the condition was found only 7 times, and then always combined with other lesions. About one-third of the cases are congenital in origin and then the disease is usually associated with some other abnormality.

The acquired form is due to a previous attack of endocarditis. It is then almost always associated with mitral stenosis. The statistics show that females are affected three times as often as males.

Symptomatology.—Cyanosis is the first symptom to attract attention, and is the most characteristic of the early manifestations. It frequently precedes all other symptoms by a year or more. In no other disease of the heart, with the exception of a congenital defect, is cyanosis such an early symptom. These patients complain bitterly of cold on the slightest exposure. Later, extreme dyspnea is present, following slight exertion, and is the chief complaint. Inasmuch as mitral stenosis accompanies the lesion in such a large proportion of cases, the symptomatology is in general similar to that of mitral stenosis. Polycythemia and clubbed fingers are generally present when the lesion is discovered.

Anasarca is a comparatively early symptom. Pulmonary congestion with prune-juice sputum is frequent. Sudden death is fairly common. Later on the symptoms of tricuspid regurgitation, such as edema, enlargement of the liver, etc., are added.

Diagnosis.—**PHYSICAL SIGNS.**—The disease is rarely recognized during life. When discovered it is usually in combination with mitral stenosis. The area of heart dulness is increased to the right. This is due to the dilatation of the right auricle.

Sometimes there is a presystolic thrill and snapping first sounds similar to those of mitral stenosis.

There is a short presystolic murmur just to the right of the sternum in the fifth intercostal space. Sometimes it is only heard over the lower sternum. The murmur of mitral stenosis, which is so commonly associated with this condition, is usually only heard over a limited area about the left nipple, and the sound grows fainter as the sternum is approached. The tricuspid murmur, on the other hand, becomes more pronounced as one approaches the mid-sternum region.

Liver pulsation occurs relatively early, and with a polygraph it can be demonstrated that this pulsation is auricular or presystolic in time. The same holds true of the jugular pulsation. Commonly the distention of the jugular veins is without visible pulsation, and without the polygraph it cannot be determined.

DIFFERENTIAL DIAGNOSIS.—The only serious question consists in the differentiation between mitral stenosis and tricuspid stenosis as both are commonly present when mitral stenosis can be demonstrated. The problem is only difficult when a presystolic or a diastolic murmur of mitral stenosis is present, and transmitted to or beyond the sternum. One must then make the diagnosis on the basis of the concomitant symptoms. In tricuspid stenosis, cyanosis is a relatively early, marked and continuous symptom, whereas it is a late symptom in mitral stenosis. Dropsy is an early symptom in tricuspid stenosis and appears late in mitral stenosis. The evidence of the polygraphic tracing may occasionally be of help, but after all, comparatively few practitioners have the time or instruments to devote to such an examination. When the murmur in rare cases has become mid-diastolic in time, it is occasionally confused with aortic regurgitation, the murmur of which is sometimes heard in the same area. The other evidences of aortic regurgitation are sufficient to prevent a mistaken diagnosis.

In a failing mitral stenosis a systolic venous pulsation, if present, is due to tricuspid regurgitation, and each time that the right ventricle contracts there is a systolic pulsation in the veins of the neck, whereas in tricuspid stenosis the pulsation occurs just before systole, and is due to a contraction of the auricle and not of the ventricle.

The diagnosis is seldom made during life, and is only possible if a complete clinical picture is present. This consists of a cyanosis of long duration, increased size of the right auricle as demonstrated by *x-ray* and by percussion, a presystolic thrill and murmur over the right sternum region, liver pulsation, and a sphygmographic tracing.

Prognosis.—In Pitt's series quoted by Osler, of 87 patients 31 died between the ages of twenty and thirty years.

Malignant endocarditis affects the tricuspid valve oftener than does the benign form of endocarditis.

The outlook usually depends upon the severity of the associated mitral lesion and upon the muscle on the left side of the heart. When this begins to fail the course is steadily downward. Compensated tricuspid stenosis may exist for several years, with several breaks in compensation; but this is not the rule. When dropsy sets in, unless it dis-

appears promptly under rest it will probably not respond to any treatment. Sudden death is fairly frequent.

Pathology and Pathological Physiology.—The changes found in the valve are identical with those found in mitral stenosis. In old cases, cirrhosis of the liver, and perihepatitis are frequently found. The pathological physiology is the same as that of mitral stenosis with the difference that the systemic veins are affected instead of the pulmonary veins.

When narrowing goes on to such an extent that the auricle does not entirely empty itself, then the contraction of the muscle of the auricle drives the blood back into the vena cava, and thus slows the circulation in the heart and lungs. As a result of this slowing the oxygenation of the blood is lessened, and cyanosis occurs. As a consequence of this cyanosis, polycythemia appears.

After the hypertrophy of the auricle becomes extreme, dilatation follows, and the contraction of the auricle can no longer be made out in the polygram as a presystolic wave. After this, no further compensation can take place, and the slightest strain or infection produces dropsy and enlarged liver.

PULMONARY STENOSIS

Etiology.—Pulmonary stenosis is almost always a congenital lesion, and, as such, constitutes a fairly large percentage of what is, comparatively speaking, a very rare condition, i.e., congenital heart disease. As an acquired lesion it is extremely rare. The causes are the same as those of the stenosis of the other valves. Of these, endocarditis is the most common.

Symptomatology.—In the acquired form there are no marked symptoms until there is some loss in compensation. In the congenital cases, of course, cyanosis is an early and consistent symptom, and is associated with clubbed fingers. With loss of compensation, dyspnea, dropsy and cyanosis are in evidence and are commonly progressive.

PHYSICAL SIGNS.—*Inspection.*—Until there is loss in compensation, there are no distinct signs on inspection. Usually, however, when the case is first seen the picture of tricuspid regurgitation is already present.

Palpation.—A systolic thrill may be felt at the base in the second and third left intercostal spaces, just to the left of the sternum. There are no characteristic changes in the pulse until tricuspid insufficiency is added, when the picture of that disease becomes evident.

Percussion.—Dulness is increased to the right as a result of the hypertrophy of the right ventricle.

Auscultation.—The diagnosis is based upon the presence of a systolic murmur heard with maximum intensity close to the sternum in the second left intercostal space. It is transmitted upward and toward the left clavicle. It is a harsh murmur and lasts through the entire systole. It gives the impression of being closer to the ear than do the other murmurs. The second pulmonic sound is very faint, or, more often, cannot be heard at all.

Diagnosis.—As an acquired lesion it is an extreme rarity, and the diagnosis may seldom be established. On the other hand, the diagnosis of the congenital form may frequently be made. The frequency with which systolic murmurs are heard at the base of the heart renders it necessary to call attention again to their relative lack of diagnostic importance. Pulmonary stenosis is the rarest cause of this murmur. A bend in the pulmonary artery is one of the most frequent causes. Next to this, anemia is the most common factor. If true pulmonic stenosis is present, the second pulmonic sound is faint or absent.

The murmur of aortic stenosis is well heard in the same area, but is transmitted up unto the vessels of the neck. The second aortic sound is faint or absent, and there is left hypertrophy, plus the slow characteristic pulse.

Prognosis.—The patients with congenital disease seldom live many years. As long as those with acquired stenosis do not present symptoms they are only in potential danger. At the onset of any well-developed signs of decompensation the progress is rapidly downward. Pulmonary stenosis impedes the blood supply to the lung, and this produces a condition which is the reverse of mitral stenosis. As a consequence most patients who survive this disease for any length of time eventually die of pulmonary tuberculosis.

Pathology and Pathological Physiology.—The postmortem changes in the valve are similar to those in stenosis of the aortic valve. In some cases the conus of the right ventricle is involved. Generally speaking, vegetations, sclerosis, and calcareous deposits occur, as in the other valves. The obstruction of the outlet of the right ventricle increases its work, similar to that occurring in the left ventricle in aortic stenosis; consequently there is hypertrophy. The right side of the heart is not, however, constructed so that hypertrophy may go on indefinitely as is the case with the left side, so that within a short time it dilates. Tricuspid insufficiency follows, with all of the evidences of broken compensation.

PULMONARY REGURGITATION

Etiology.—This is an extremely rare lesion. Up to 1910 Norman Pitt was able to collect only 10 undoubted cases in the literature. It occurs as in the other forms of regurgitation, (1) as a result of endocarditis (of which the gonococcus has been the exciting cause in one-half of the recorded cases) or, (2) due to the inflammatory change associated with aneurysm of the aorta, (3) rarely, as a congenital lesion, or (4) as a relative insufficiency. This relative insufficiency follows or is associated with any great increase in pressure in the pulmonary artery. It is most commonly found in association with the disease producing this back-pressure, as in mitral stenosis and chronic emphysema. When it is associated with mitral stenosis it is thought by some to produce the Graham Steele murmur.

Symptomatology.—Unless there has been a break in compensation there are no distinctive signs of the disease. The most characteristic symptom is dyspnea, but dyspnea on exercise is such a common symptom in cardiac disease that it is in itself of little diagnostic value. In this disease it sometimes occurs in paroxysms without any evident cause. The slight cough which accompanies any pulmonary congestion is usually present in all of these cases.

Sepsis, particularly gonorrheal sepsis, has an affinity for this valve, and it should be examined in all cases of septicemia.

PHYSICAL SIGNS.—*Inspection.*—The associated lesion commonly masks most of the physical signs. On inspection cyanosis is sometimes found to be present. The evidences of the dilated right ventricle and conus arteriosus, as shown by the pulsation in the second and third interspaces, as well as in the epigastrium, are usually present.

Palpation.—When dilatation has taken place pulsation may be felt in these above-mentioned spaces. The diastolic thrill is rare. Dulness on percussion can be made out to the right of the sternum.

Auscultation.—The diastolic murmur is the most distinct sign of the disease. It is best heard at or near the left second costal cartilage. Occasionally it is best heard an inch or two below this point. It is not transmitted to any extent, and then only downward. It gives one the impression of being near the ear. Usually it is a soft, blowing murmur.

Differential Diagnosis.—The condition rarely presents diagnostic difficulties. It is easily differentiated from *aortic regurgitation* because of (1) the absence of marked left-sided hypertrophy, (2) the absence of the Corrigan pulse, and of the great pulse-pressure, (3) the absence of transmission to the vessels of the neck, and (4) the other incidental signs of aortic regurgitation.

It is true that the murmur of aortic regurgitation is frequently heard in the same location, but it is generally transmitted up to the right and down. In any case in which aortic regurgitation is present, it is almost always the predominant lesion, as far as physical signs are concerned. Nearly always when the diagnosis of pulmonary regurgitation is made on the basis solely of a diastolic regurgitant murmur, it will eventually turn out that the case is one of aortic regurgitation.

It is in connection with *mitral stenosis* that most difficulty may be encountered. In uncomplicated mitral stenosis the murmur is never heard so far up on the chest-wall. The slapping first sound, the reduplicated second sound, and the thrill—one or more of these sounds will always be present—serve to differentiate these cases. The Graham Steele murmur may be considered a functional pulmonary regurgitation. It is uncommon, confined to a small area and indistinguishable from organic pulmonary regurgitation.

Prognosis.—Here the prognosis depends upon the cause of the lesion. If it is due to relative insufficiency, consequent on other lesions, the outlook is not immediately serious. The prognosis must rather be based

upon the condition of the right ventricle. If it reacts without pronounced decompensation, freedom from the immediate danger is assured.

Organic disease producing regurgitation is so commonly acute and so rarely chronic that little information is available upon which to base a prognosis. In general, however, it is to be predicated on the condition of the right ventricle, and consequently on the increase of tricuspid regurgitation.

Pathology and Pathological Physiology.—The mechanism of the production of this murmur is exactly similar to that of aortic regurgitation, except that the blood flows back into the right ventricle instead of into the left ventricle. Some hypertrophy of the right ventricle always follows. It is rarely an uncomplicated lesion, so that the postmortem changes are not distinctive.

By far the greater number of cases are due to functional dilatation and the microscopical changes are not very decided. The conus arteriosus and the right ventricle are dilated. There are other changes throughout the vascular system, but they are the same as those met with in broken compensation from any cause. Most of the cases are transient. One looks for the lesion most commonly in association with mitral stenosis.

GENERAL PROGNOSIS OF CHRONIC VALVULAR DISEASE

In view of the general consensus of opinion that in the late war soldiers who had valvular lesions and who had never developed signs of decompensation were just as efficient from a military standpoint as others, it seems unorthodox to maintain that such patients do not have as good a general outlook as to length of life as those with healthy valves. One constantly sees patients who have been rejected by insurance companies many years ago, and yet to-day are seemingly healthy and well; yet in the main it is these exceptions to the general rule which attract our attention. The cumulative clinical experience of the profession is to the effect that a large percentage, certainly more than a majority of patients with unmistakable organic valvular disease, sooner or later present signs of decompensation. When the valves are diseased, muscular disease, also, is always present to some degree. The heart may functionate properly for some years, until added infection puts a strain on it and decompensation occurs. The extra labor of the army and camp is not nearly as apt to bring this about as are the infections of civil life. The experience of the army has been that these patients were as strong as others, but that when a slight infection of any kind, particularly in the respiratory system, occurred, they commonly broke down.

Aside from its import in general practice, this matter of a proper evaluation of the significance of valvular disease becomes a vital one in life insurance examinations, and in industrial life. The necessity for a yearly examination of men who hold positions of such a nature that their sudden incapacitation would menace the life of others is quite apparent to all. Such men as engineers engaged on railway trains, boats

or vehicles of any kind, boiler-men, motormen, conductors, switchmen, tower-men, elevator-men, telegraph and signal operators, chauffeurs, pilots, etc., are all in this category. It may be argued here that one might gauge their future health and reliability by the presence or absence of symptoms, at the time when they present themselves for a position, but such candidates are at pains to disregard or conceal any or all symptoms. For that reason the only practical solution is to rely upon such signs as are found on a rapid physical examination and to apply general principles of prognosis based upon these findings. As a general rule those who have a definite cardiac lesion should be prevented from engaging in any of these occupations even though individually the patient may be a good risk, because after all there is a slight appreciable risk in all of these cases. Insurance companies are often criticized for their attitude in this matter, but after all these companies are not organized for charitable purposes but rather to take only selective risks as far as human judgment can determine them, and no one can maintain that the subject of valvular disease is entirely normal.

The question which the patient usually asks on being told that he has a valvular lesion is, "Can I ever get well?" and in his mind he stores away at once the picture that there is a likelihood of sudden death for him. In answer to the first question one is justified in saying that practical recovery may be assured but that absolute recovery is a physical impossibility. The figure of speech that a face with a scar is quite as useful and quite as long-lived as one without a scar is a homely yet intelligent word picture which makes clear the relative harmlessness of the lesion; or again, the following picture sometimes makes it more clear to the patient's mind: "There are two trees of equal size and strength. A woodman makes a gash in one; it heals over, leaving a scar. Both trees are to all intents and purposes the same, as far as strength, seed-bearing properties, etc., are concerned, and continue so for years, but a severe storm is more apt to blow the injured one over than the sound one, because of the initial scar of many years previous. If the storm is a very severe one the perfect tree as well as the injured one is apt to be blown over." As a consequence of the lesion, with ordinary care the patient's life will not be shortened in the long run. At the examination his mind should be disabused of the idea that he has a weak heart. This is a term employed by some practitioners to explain the symptoms of muscular insufficiency, and by others as a means of conveying to the patient's mind the fact that he has an organic valvular disease, but in an endeavor to assuage his mind gives it this term. It generally serves to make the patient feel that the disease is not organic, and is only of a temporary nature. It is an elastic term which seldom conveys to the minds of any two patients the same picture, or the one intended by the physician.

The second question should be always discussed with the patient as soon as the diagnosis is made. He should be told that he has a valvular disease, but that he will not die suddenly. The prognosis, no matter what the lesion may be, can never be made with exactness. The best

statement that can be made is that death is or is not imminent; in fact, the future prognosis can only be made with the addition of many "ifs." One may divide the prognosis as follows: (1) the ultimate prognosis, (2) the immediate prognosis, (3) the mode of death. Of course, this should not be fully discussed with the patient. The *ultimate prognosis* is of importance, for ahead looms the possibility of change of occupation, and the question of marriage and pregnancy. In the young the questions of exercise, and sports, climate, etc., must be considered.

The *immediate prognosis* has to deal with the problems presented when there has been more or less evidence of failing compensation. Very many more factors enter into this problem than into the first mentioned.

The third question is that of the *mode of death*, and the possibility of sudden death. While the mode of death can often be foretold, the question of the likelihood of sudden death is always perplexing, inasmuch as the changes which immediately precede this event are microscopic rather than macroscopic.

In general, one may base the ultimate prognosis of heart disease upon five general conditions:

- (1) The ultimate cause of the heart lesion.
- (2) The condition of the arteries and kidney.
- (3) The portion of the heart involved.
- (4) The person who has the disease.
- (5) The treatment he receives.

From a prognostic standpoint it may be stated that symptoms are of far more importance than physical signs.

Cause of Cardiac Lesion.—The ultimate causes of cardiac lesions as seen in active hospital service may be roughly grouped as follows:

Rheumatic	70 per cent.	<i>Cabot estimates thus:</i>	
Syphilitic	15 "	Rheumatic	45 per cent.
Arteriorenal	15 "	Syphilitic	12 "
Secondary to diseases		Nephritic	20 "
in other organs (lungs,		Arteriosclerotic	15 "
thyroid, etc.)	5 "	Goiter	5 "
Congenital	negligible		

RECURRING "RHEUMATIC CARDITIS."—Acute cases in children with fever, particularly those with pericardial involvement, are always serious. Those *without* temperature elevation over 100° F. (37.77° C.) are not in any immediate danger. It is only in the case of those presenting considerable temperature elevation and severe general symptoms that we need worry as to the immediate future.

RHEUMATIC FEVER.—Rheumatic involvement of the heart offers a favorable prognosis as compared with other forms of heart disease. This is particularly true when the valves are the portions of the organ which are the most affected; in such cases the patient is forewarned to

keep quiet, and no such warning is given in silent cases. The effects on the myocardium are more transient than in other infections, but are more apt to be repeated. Therefore, the older the patient is at the first break in compensation the better is the outlook, for reinfection is correspondingly less likely. As a rule such hearts have from 15 to 20 breaks in compensation before the fatal termination occurs. They may go on for years functioning quite well after one or more break-downs which because of the presence of extreme edema, hemorrhage, etc., are so severe that life is despaired of.

The presence of infection of any kind is usually the determining factor in the break-downs. Consequently the less frequent any such infection is, the less likelihood there is of a fatal termination, and, on the other hand, the more subject the patient is to such infections the more rapidly the end comes. The course of the lesion is a series of repeated acute attacks rather than a steadily progressive process.

SYPHILITIC CASES.—As a rule the early syphilitic manifestations are not serious. The heart or vessels are involved in 50 per cent. of all cases of syphilis. Its effects are positive and generally progressive, unless treated.

In heart disease due to *untreated* syphilis one may tell the patient that the lesion occurred about fifteen years before the onset of the symptoms, and warn his friends that he has at most three years longer to live. Treatment is only palliative.

In *treated* cases, of course, this general rule does not apply, about five years being the ordinary period of life expectancy after the onset of symptoms. Once symptoms are manifest, they may be ameliorated, but it is impossible to dissipate the permanent organic changes. With the exceptions of gumma, treatment is only partially successful. The symptoms may be modified, especially if the pain is due to lues, and life will be prolonged, but tissues cannot be made over again, as is the case in some other parts of the body, in which syphilis reacts marvelously to treatment. Frequently improvement is only noticeable after some months of treatment. If marked broken compensation has already occurred, the patient seldom lives more than one year, and usually much less. The number of recoveries from attacks of decompensation is rarely more than three, differing from rheumatic carditis, from which there are so many recoveries after breaks in compensation.

ARTERIOSCLEROTIC FORM.—Cases associated with high blood-pressure are so closely related to kidney disease on the one hand or to syphilis on the other, that it is difficult to lay down dogmatic rules as to progression. If the high blood-pressure is a family trait the course of the disease is likely to follow whatsoever course the family mode of death has usually been due to, *i.e.*, one of the material accidents, as (1) cerebral hemorrhage, (2) nephritic death, or (3) cardiac death, each running its own course. In general the outlook is fair if the lesion is due to something which can be corrected by hygiene or medicine. If it is due to renal disease there will be a steady progressive advance. The

height of the pressure is not of so much import as its course. If it steadily rises in spite of everything the outlook is unfavorable. A marked fall in pressure without cardiac improvement is serious. Stout patients with high blood-pressure, dyspnea, and traces of albumin look like hopeless cases, but if they can take care of themselves they often live for years. Any infection, however, is likely to carry them off. The author believes that in the past we have viewed these cases too seriously. The more experience one has the more hopeful one becomes as to the outcome. Cases which are progressive during the first few months after the onset of the symptoms are apt to progress badly, but these are comparatively rare. In cases which are slowly progressive, with intervals of well-being, if properly treated, live for many years, and, in some instances, they may even go back to strenuous occupations provided a long rest is enjoined. In general, the better the financial status of one's clientèle the better the prognosis in this group, because the patients are better able to take care of themselves and do not have to worry about the necessities of life. The hospital patient who suffers from high blood-pressure and valvular disease does not long survive his first attack of decompensation.

Kind of Person Who Has Heart Disease.—The man who can take things easy and who readily learns a lesson always has an advantage over his nervous and fretful brother. Heredity and environment are two great factors which must always be considered in making the prognosis.

HEREDITY.—Aside from acute infectious attacks, heredity counts for more than anything else. The patient whose family history is free from cardiac disease has a much better prognosis than the one whose progenitors have had the disease. A family tree with one or more roots involved by cardiac disease means that the infection has been passed on, or at least that the susceptibility to the rheumatic poison is established in the offspring. Such patients are more apt to have severe attacks. The *anemia* which is present in all victims of cardiac disease is an index of the patient's reacting power to the virus, and of course his heart-muscle is correspondingly affected. In the case of those who suffer from severe anemia the disease is apt to be serious and the heart-muscle is correspondingly deprived of rich blood, in other words, pale cardiac patients are apt to die. If anemia occurs for the first time in the course of an acute exacerbation, grows steadily worse and does not react to treatment, it is sure that the patient will not long survive. This is especially true in aortic regurgitation. On the other hand, if it appears late, and reacts to treatment, it has no evil prognostic import.

ENVIRONMENT.—The presence or absence of repeated infection, susceptibility to cold in the head, chest or tonsils, are all grave handicaps. A head cold or a tonsillitis often causes an attack of fever in these patients, and frequently precipitates a fatal issue. The presence of chronic foci of infection, such as teeth, tonsils, sinuses, prostate, uterus, etc., is a factor to be weighed seriously. Nor must the condition of the stom-

ach and digestive tract be disregarded in arriving at a conclusion. Ability to sleep is always a good omen, no matter how threatening the case may otherwise be.

OCCUPATION.—Occupation is of prime importance, although the author believes that it is of less importance than frequent mild infection. Certainly the continuance at any occupation or work which induces any of the symptoms of disturbed compensation must be weighed seriously.

CLIMATE.—In general the prognosis is worse in the winter and in the cold weather than in the summer. The same rule applies as to climate in general. Damp, cold climates are much less favorable than dry, warm climates.

AGE.—In young children the outlook is unfavorable; not only do many such patients die of acute carditis, but they are apt to have repeated attacks which damage the valves irreparably. Endocarditis in a child under six years of age, if associated with symptoms, usually foreshadows a ruined life. Combined valve lesions are also very serious, because malignant endocarditis is more likely. In elderly patients the outlook is better, because the older people take better care of themselves. Old hearts are more easily trained than young ones. Worry and excitement have a very bad effect, and lead to breaks in compensation, especially in aortic disease. In such cases the usual sequence of events is:

- (1) Symptoms of coronary lesion.
- (2) Nephritis.
- (3) Myocardial weakening.

The three parts of the circulatory tree, heart, arteries and kidneys, are so closely related that injury to one is practically always the concern of all. The condition of the arterial system is of as much import as the condition of the valves of the heart. As long as the arterial system is in good condition there is little cause for alarm. This is usually the case in compensated mitral disease, and is one of the chief reasons for its comparative harmlessness. When young patients show signs of arterial involvement the outlook is indeed gloomy. In those over fifty years of age the presence of sclerosis is not of so much import. The older the patient the better the outlook. Death from cardiac disease is more common among those of middle age than among the aged.

The kidney forms the third root of the trilogy, and while it is of relatively less importance than the heart or arteries during the early periods of life, in the case of those advanced in years it is of quite as much import. When decompensation occurs in a patient with a contracted kidney the result is more hopeless than is the case when any other single complication is present. If the kidney is large and white, almost any severe inflammatory disease nearly always leads to an immediate fatal termination. This is especially true when the valve lesion is that of aortic regurgitation. Generally speaking, primary kidney disease which presents dyspnea on exertion as an early symptom produces death from cardiac insufficiency.

The earliest sign of broken compensation is the presence of fine râles at the base of the lungs when the patient sits up after having been in a recumbent position for some hours.

Another way of determining the onset of broken compensation is by the disappearance of the pulse when the arm is elevated above the head. Abrahams has called attention to the fact that in mitral disease, usually before there is a break in compensation, the pulse can be felt as well in the elevated arm as in the lowered arm. At the first sign of failure, there is a marked difference in the quality of the pulse in the elevated arm. When there is a decided break in compensation the pulse in the elevated arm disappears entirely. Of course the weakening of the second pulmonic sound is a positive evidence of impending failure, and is, when it can be determined, of more consequence than any other of the signs mentioned. In this case, symptoms are of more importance than physical signs. Dyspnea is the most valuable single symptom as a basis for prognosis. Cheyne-Stokes breathing, although not serious in itself, is of evil import, and the patient seldom survives for long, if it becomes noticeable during waking hours. If it disappears and is followed by rapid breathing, death is not far distant.

Conditions Affecting the Prognosis.—**MURMUR.**—*General Considerations.*—The relative softness or loudness of a murmur has no significance, although, in general, the murmur which was soft and becomes harsher is a good omen, as it indicates an increased muscular force. And, per contra, the loud murmur which does not entirely displace the first sound of the heart in mitral regurgitation is a good sign. One which does not entirely displace the second sound of the heart in aortic regurgitation is also a good sign. A loud and well-transmitted murmur, even though it entirely displaces the second sound of the heart at the apex or at the base, has a fairly good prognosis. Occasionally, in children who are rapidly growing, this does not hold true. A weak murmur which reacts to digitalis and remains loud, indicates that there is no immediate danger. When such a murmur becomes strong on digitalis stimulation, but quickly returns to its former state, the outlook is not encouraging.

The average length of time from the formation of a lesion to break in compensation has been variously stated as from seven to fifteen years.

COMBINED LESION.—When these are on the same side of the heart, they are worse than when on opposite sides.

The most dangerous combinations in order of frequency are:

1. Aortic regurgitation and mitral stenosis.
2. Aortic stenosis and mitral stenosis.
3. Aortic and mitral regurgitation.
4. Mitral regurgitation and mitral stenosis.

In passing it is well to point out that it is unsafe to diagnosticate involvement of more than two valves in any patient.

The last three are fairly common, and are of course very much more

serious than single lesions, as it stands to reason that the myocarditis is much more extensive.

Patients suffering from grave heart disease will sometimes pass through a serious infectious disease, but during convalescence they are apt to go to pieces. This is especially true in *pneumonia*. They frequently pass the crisis satisfactorily. Patients with valvular disease, but who have not had any evidences of broken compensation, usually recover from ordinary lobar pneumonia in approximately the same proportion of cases as among normal individuals. In those, however, who have previously shown decided symptoms of decompensation, recovery is uncommon.

Bronchitis in a patient with valvular disease always requires serious watching. It is almost as grave an infection in a patient who has shown signs of decompensation, as an ordinary pneumonia in a previously healthy individual.

When *bronchopneumonia* occurs it is usually a terminal event. When true epidemic influenza attacks a cardiac patient who has suffered from broken compensation, it is accompanied by a very slow convalescence, which must be measured by months rather than weeks, and the patients rarely ever completely recover. If bronchopneumonia occurs, death is the rule.

In *erysipelas*, when there is no disturbance in compensation, the outlook is favorable. When decompensation is present it is a very serious complication. Acute *pericarditis*, even with extensive effusion complicating an old valvular lesion, generally presents a good prognosis, although it is apparently a very desperate combination.

In general the outlook is favorable in *pregnancy*. If compensation has been broken it is a serious problem. When mitral stenosis is present the outlook is much worse than in the presence of any other valvular lesion. Especially is this true with regard to the infant. Death may occur suddenly toward the end of pregnancy, and usually comes on as the result of pulmonary edema. Early in pregnancy physiologic abortion is the rule. Labor itself does not add greatly to the strain of the heart, and is not in itself of serious import.

Jaundice, if hemolytic, is a bad sign.

Acute *inflammation of the gall-bladder*, just as any other infection, is often the cause of a fresh attack of endocarditis and death.

Psychoses, when they occur with aortic disease, are not immediately serious. When they are marked in mitral disease they usually indicate that death will occur within a few weeks.

Dropsies, if not of long standing, commonly result, at least during the early attacks of decompensation, in recovery, and the patient may live for years, but when there is fluid in the serous cavities, it does not rapidly disappear. The patient does not usually survive for many months. As far as immediate improvement is concerned the public hospital patient has in general a better outlook than the private patient, because he has not been under treatment and has been living an unhy-

gienic life, and may therefore react satisfactorily to more favorable conditions. The reverse is true of the private patient, who has, in many instances, already used all of the therapeutic resources and has had most of the advantages of proper life and surroundings, without avail.

The patient who does not promptly react to rest in bed, opiates, and two or three days of intensive digitalis therapy, generally offers a grave prognosis. If improvement occurs after rest in bed alone, the outlook is not as favorable as it is if it follows the use of digitalis. It is difficult to account for this on a physiological basis, but this is a clinical observation. In general the pulse-pressure increases, and the frequency is reduced in all except the aortic cases as the patient improves, and *vice versa*. A decompensated heart-beat which does not fall below 90 after prolonged, careful treatment during two months will probably never result in recovery.

When heart-failure cells are found in the sputa the disease is far advanced. Spitting of blood is not serious if the compensation is good, but when it is very profuse and continues for several days, recovery is the exception. The same is true to a lesser degree in the case of nose-bleed.

Infarcts are always dangerous; if septic, they are fatal. About one-third of all patients with cardiac involvement have at some time or other suffered from such infarction.

Unless fluid is present, *pleurisy* is not of much significance.

In early broken compensation the immediate prognosis depends upon:

- (1) The extent of stasis in the lungs. This can be measured by:
 - (a) The amount of dyspnea and the inability to take a long breath.
 - (b) Cyanosis.
 - (c) Râles at the base of the left lung after the patient has been lying on his back for some hours.
 - (d) The condition of other organs: the size of the liver, and the quantity of urine.
- (2) The condition of the auricles:
 - (a) Size, dilatation, measured by the extent of dullness in the cardiohepatic angle and at the base of the heart.
 - (b) Functional activity—*fibrillation*. This generally indicates that the patient has on the average about five years to live, seldom more than ten. The older the patient when the fibrillation occurs the better the outlook.
- (3) The condition of the ventricles, especially as to the presence of high arterial tensions, bronchitis, and other complications.

Commonly death is a slow process in heart disease. It is usually associated with pulmonary edema, and in almost every instance there is

some terminal infection, generally a pneumonia or nephritis, less frequently an acute endocarditis or enteritis. Usually death is brought about through an added disease of some other organ. If the condition is acute it is to be assumed that the lungs are responsible; if it is chronic, that the kidney is to blame. Sudden death without any warning may occur in any form of heart disease, but it is comparatively rare. Nearly always there are warning signs within a few days before the fatal issue, although these warnings may be so slight that they are commonly overlooked. Aortic regurgitation furnishes the largest quota of sudden deaths without any marked warning, but even here there may be danger signals in the shape of attacks of stenocardia. About 40 per cent. of cardiac syphilitics die suddenly, and this is one of the frequent causes of sudden death without much warning. In about 2 per cent. of the cases of mitral stenosis the patients die suddenly. In the latter case, death usually occurs in a patient who is in bed during the attack of broken compensation and who is apparently doing well. On sitting up suddenly he falls over dead. In mitral cases an x-ray picture of the heart lying flat on the diaphragm is the only physical sign which gives warning of such a possible ending. A sign of some value in a patient who has not been under digitalis is as follows: One hears the two sounds of the heart. After the second sound one wonders if the heart will ever beat again, the interval being so long and the rhythm seeming to have stopped. This same phenomena is also present in a heart thoroughly digitalized. Many of the patients suffering from mitral stenosis die of embolism, especially cerebral embolism. In such cases death is not sudden. In pulmonary embolism death is also delayed, usually for from fifteen to twenty minutes after the onset of the embolism.

Angina pectoris is the disease commonly associated with sudden death and yet, as compared with the frequency of the affection, it is not so immediately fatal as was formerly taught. It is, however, always a step toward sudden death. In any case of heart disease, with severe pain about the heart, even though it has none of the characteristic radiations of angina pectoris, if the pain is not speedily relieved by large doses of morphin a fatal issue within a few hours is at least a strong possibility. Repeated attacks of cardiac asthma, which is another term for acute suffocative pulmonary edema, in conjunction with symptoms of vomiting, diarrhea, delirium, and marked mental wandering, often foretell the near approach of death, but it is relatively seldom that these patients die during the attack of acute pulmonary edema itself.

Large, stout patients with small hearts lying flat on the diaphragm, accompanied by a weak and rapid pulse, a systolic murmur at the base, and a general arteriosclerosis, are most liable to die suddenly. The minor symptoms of which these patients complain are not apparently any worse just preceding death than they have been for weeks and months previous, but on close questioning it will be found that some unusual strain has been placed on the heart just preceding the fatal

issue; this is commonly a large, indigestible meal or some physical exertion, such as running up stairs, or some anxiety.

GENERAL TREATMENT OF VALVULAR DISEASE

CASES DISCOVERED BY ACCIDENT AND PRESENTING NO SYMPTOMS

When in the course of a physical examination one meets with a patient who has a valvular lesion with or without a history of a break in compensation, and who yet presents absolutely no symptoms when examined, what course should be preferred?

Of course no one will advise medicine for a patient who presents nothing but a murmur of which he may or may not be conscious. From a practical standpoint, however, the patient should be informed of the presence of the murmur, with a proper explanation of what it signifies (*see* General Prognosis). This opens up a large question. That patients occasionally suffer much worry and annoyance from such a knowledge is undoubtedly true. On the other hand, no one can deny that it may be of more lasting value to the patient, as far as life itself is concerned, if he knows that a cardiac lesion is present. The worry may annoy him, but it will not materially shorten his life. It is customary to say that there is no danger—to a man who has a compensating valvular lesion—but experience teaches us that sooner or later, due to either a fresh disease of the valves or to strenuous exercise, most of these patients will (if they live long enough) become victims of broken compensation. Thus, a patient with a valve lesion is a potential cardiac invalid, no matter how well he may be at the present time.

He should be taught the seriousness to him of slight infections, inasmuch as they are always more likely to light up trouble in his valves than in those of a normal individual. He should also be warned not to undergo severe physical strain. On the other hand, there is no indication to lessen the ordinary duties of his avocation. If the patient is a child and does not present shortness of breath or palpitation on strenuous exertion, no special restriction as to ordinary games is necessary. He should be prevented, however, from taking part in the strenuous forms of exercise, such as football, rowing, running, etc. His occupation should be selected so that hard labor will be avoided. In all cases in which such a lesion is discovered general directions should be given to prevent a recurrence of the disease which is primarily responsible for the valvular lesion. If syphilis is the cause, the systematic yearly use of **antiluetics** and the **avoidance of alcohol** (*see* Treatment of Broken Compensation) are important. If arteriosclerosis is the cause, the employment of a suitable **dietetic and hygienic regimen**, and the intermittent use of **potassium iodid** should be instituted.

Inasmuch as fully two-thirds of the cases of valvular disease met with in practice have their origin in previous attacks of rheumatic endocarditis, it will be admitted that the **prevention of rheumatic**

endocarditis is the most logical step. Unfortunately the contagiousness of acute rheumatic fever and of the endocarditis which follows it is not sufficiently appreciated by the profession. The author has scarcely ever met with a frank case of rheumatic fever or rheumatic endocarditis in a child which could not be traced to a previous infection in the rheumatic parents, grandmother, nurse, or some one who had charge of the child. In adults it is more difficult to trace the infection.

The history of exposure is almost, if not quite, as important as it is in tuberculosis, so that the first step in prevention is to prohibit any one who is suffering, or who has suffered, from rheumatic fever from coming in constant and close contact with small children. In practice an old grandmother is the common carrier of infection.

Once the patient has been infected with the virus of rheumatic fever, the condition in that individual is somewhat analogous to one infected with lues, in so far as that symptoms are apt to reappear whenever there is a lowering of the resistance from any cause—whether it is infection, worry or overwork—so that “once rheumatic, always rheumatic.”

The most common cause of the relighting of the rheumatic endocarditis is a head cold, tonsillitis, or pharyngitis; therefore the first consideration of the greatest importance is the **elimination** of such **common infections**. These common infections are more apt to occur in patients suffering from diseased tonsils, adenoids and deflected septa. As to focal infection itself, there is no positive evidence that **removal of tonsils, adenoids, teeth, or any other focus**, prevents recurrence of acute rheumatic endocarditis as such—except in so far as it lessens the likelihood of infection from those sources.

That the removal of infected teeth and such foci is followed by freedom from attacks of endocarditis or rheumatic fever is quite true, but, inasmuch as such infections fail to recur under other conditions there is no scientific proof as to their cause and effect. However, if the removal of enlarged tonsils, adenoids and deflected septa does have a positively good effect, it is because it lessens the chance of acquiring fresh infections, and the frequency of breaks in compensation depends in direct proportion upon the number of such infections. In other words, no infections—no fresh endocarditis—no loss of compensation. This is a working rule which is not absolute but is practical, as all who have had endocarditis are likely subjects for fresh attacks, and consequent breaks in compensation. Such patients should be under **frequent observation** at stated periods throughout the year. In this way only can the minor symptoms be noted, and advice given so as to prevent major breaks in compensation. The same advice holds good to a greater degree for those who have had an attack of lost compensation.

This becomes an economic subject of great importance from the hospital standpoint. A patient who has had a break in compensation, and recovers, sometimes goes back to the same environment and work

after his discharge. Sooner or later he has a relapse, so that he is seldom out of the hospital for more than three or four months at a time. This is an economic loss both to the wage-earner and to the public. To prevent this, such a patient, upon his discharge, should be instructed to return to his physician at least once every two months for instruction and advice, no matter how well he may be. If the above picture is presented to him, his coöperation may be secured.

In this way the number of hospital days in the life of a cardiac patient is less than one-fourth of that which would otherwise obtain. Incidentally he is able to support himself and his family that much longer, and prevents them from becoming a charge on the community.

Cardiac clinics are of even more practical value than the tuberculosis clinics now so generally utilized, because prevention of loss in compensation in cardiac patients is a far more practical achievement.

Outline of Treatment of a Case of Valvular Disease

(When discovered by accident with or without the history of previous loss of compensation)

No Symptoms Present:

- (1) Occupation—work to depend upon the reaction to exercise.
- (2) Long period of convalescence, when recovering from recent attacks.
- (3) Selection of climate and delimitation of exercise.
- (4) Clothing of wool, to prevent return of rheumatic fever, avoidance of dampness, bed treatment for even the mildest infections.
- (5) Food—plain and such as is not likely to produce flatulence.
- (6) Regular bowel action—aloes or cascara as required.
- (7) Treatment of any form of rheumatism by salicylates.
- (8) Tonics as required—iron, arsenic and cod-liver oil.
- (9) No restriction on tobacco or coffee if used in moderation.

CASES PRESENTING MINOR SYMPTOMS WHICH ACCOMPANY VALVULAR DISEASE

In practice the murmur is most commonly discovered in patients who present themselves for the treatment of what appears to be a minor complaint in some other part of the body, perhaps far removed from the heart—a symptom which at first sight may have little direct connection with the heart. The evaluating of the relation existing between such symptoms and the heart as a cause constitutes the highest art in medicine. For instance, one must not jump to the hasty conclusion that, because a murmur is present in the heart, the presence of the gastric symptoms complained of by the patient is necessarily a consequence of this lesion; but on the doctrine of chances it is very likely, unless there is direct proof that there is no such connection. In most

cases the major cardiac symptom can be handled by the tyro perhaps as well as by the most experienced practitioner. It is in the management of the minor symptoms that experience is of value. Here the difference in success lies not so much in the difference of remedies employed as it does in their proper dosage and attention to detail, particularly in the matters of diet and hygiene, and in the prompt recognition and relief of these minor complaints. In the type of cases now under consideration the onset has usually been slow and gradual with slight exacerbations. Treatment even here should begin with absolute rest in bed for a period of several days. This entails the taking of meals in bed and the use of a bedpan if possible. The patient seldom feels that his complaint is sufficiently severe to warrant such a measure, but infinitely better results are obtained in the treatment of any of the symptoms by this measure than by half-hearted proceedings, such as partial rest and the internal administration of medicine. One of the chief reasons for the success of the specialist in cardiology, as well as in any other special brand of medicine, is that patients willingly go to bed at his suggestion, whereas they do not care to do so when such advice is given by their family physician. Yet they would often follow such advice if the physician were firm and positive in the matter. Absolute rest in bed for at least three days constitutes the best initial prescription for all such minor symptoms. Medicines may be used as an adjuvant and will be considered later under the Treatment of Special Symptoms. This physical rest must be supplemented by mental rest. Visitors should be barred, and only absolutely necessary reading should be permitted.

Special Indications.—The value of the **salicylates** in arresting the consequences of rheumatic disease in the heart has **not** been proven. Unless there are undoubted evidences of rheumatic fever, they are not indicated, as they commonly upset the digestive tract. The cases associated with arteriosclerosis and discovered before the onset of major symptoms offer a wide and fruitful field for the introduction of hygienic and dietetic therapy. (*See Treatment of Arteriosclerosis.*) Here small doses of **mercury and iodid** should be administered from time to time. Experience has shown that even where there is not the slightest reason to believe that lues is present beneficial results frequently follow their use, even though we cannot give a satisfactory pharmacological explanation. It is at this stage of the disease that the victims of valvular disease due to syphilis are usually brought to our attention. When there is a well-marked history of previous infection, whether or not there has been a positive Wassermann, the patient should be subjected to vigorous **antisiphilitic treatment**.

Very often the relation between syphilis and the present valve lesion is not so clear. The Wassermann reaction, when present, is of course conclusive of former syphilis, but a very large percentage of undoubted syphilitic cardiac lesions are associated with a negative Wassermann so that only positive tests should be counted. It is, of course, possible

for a patient to have syphilis and an added infection of rheumatic fever or arteriosclerosis from other causes. In such cases one follows the teachings of clinical experience. The presence of uncomplicated aortic insufficiency, unless there is positive evidence to the contrary, warrants the use of antiluetic treatment. The same holds true to a lesser degree as in the case of aortic stenosis. While the combined mitral and aortic lesions are commonly rheumatic, yet even here as well as in uncomplicated mitral disease late investigations show a high incidence of syphilis. In all cases in which there are luetic lesions in other parts of the body, particularly in the shape of small white luetic scars in the mouth running down to the edges of the lips (and these should always be looked for), areas of leukoplakia, or hardness of the testicles, luetic treatment should be administered. In any case in which there is a history of syphilis, even though the lesion is unquestionably non-luetic, the patient should have the benefit of antiluetic treatment. On the doctrine that once syphilis occurs there are always traces of it, every patient who has once been affected and who now suffers from valvular disease should have the benefit of treatment. In those cases in which only pain and slight dyspnea on exertion have been evident, the use of **salvarsan** has been found most satisfactory. The dosage should begin with 3 decigrams (4.63 grains); after this 6 decigrams (9.26 grains) may be administered. One begins with this small dosage because occasionally cardiac patients do not bear the drug well. When serious accidents occur, a coincident involvement of the arteries and kidneys is usually responsible; hence, before the administration of the drug a careful urinary examination is an absolute *sine qua non*. The author feels that the relative efficiency of this drug and its methods of administration may be rated as follows:

- (1) Intramuscular injection of salvarsan, or equivalent.
- (2) Intramuscular injection of neosalvarsan or equivalent.
- (3) Intravenous injection of salvarsan.
- (4) Intravenous injection of neosalvarsan.

The great drawback to the use of the intramuscular method is the severe pain at the site of injection, which incapacitates the patient for two or three days. The neosalvarsan is much less painful than the salvarsan. Either of them may be suspended in a solution of a neutral oil, such as oil of sesame. If **iodopin** (which is a mixture of oil of sesame with iodine) is employed, it can be readily prepared by any one, without preliminary sterilization. It should be rubbed up in a sterile mortar, drawn into a sterile syringe with a large caliber needle (No. 20), gently heated, and injected. One-half of the dose should be injected into each gluteal region close to the mid-line. Despite the drawback of pain the eventual result is so much better that, in refractory cases, its efficacy more than counterbalances the discomfort. Furthermore, the dose does not require frequent repetition, as is the case when the intravenous route is employed. Where less intensive measures are required ampoules of sal-

varsan or neosalvarsan may be readily obtained containing 1 decigram (1.543 grain) made up with a neutral oil, which may be injected weekly exactly as if mercury salicylate injections were being given; they are not much more painful than the mercurial injections and are very satisfactory.

ARTERIOSCLEROSIS.—In all cases of valvular disease associated with high arterial tension, small doses of mercury with potassium iodid should be administered in addition to dietetic and hygienic measures. In refractory cases of undoubted rheumatic mitral disease, wonders are sometimes wrought in this way. It is in these refractory cases, as well as in all the cases which are not clearly and definitely luetic, that the older specific remedies are especially indicated. Without a definite luetic history or a positive Wassermann, one would be loth to give an intravenous injection of salvarsan. In using potassium iodid and mercury in cardiac cases the initial doses should be very small, 2 grains (0.130 gram) of potassium iodid, and 1/32 (2 milligrams) of bichlorid or its equivalent three times a day, gradually increasing up to 10 grains (0.65 gram) of potassium iodid and 1/20 grains (3 milligrams) of bichlorid of mercury three times a day. Sometimes tablets of gray powder, 1 grain (0.065 gram) t.i.d., are efficient. In administering these agents, the startling results so commonly following their use in syphilis in other parts of the body are rarely in evidence. Except for the relief of pain which the iodid so commonly accomplishes, little appreciable result is apparent until after a month or two of treatment, sometimes not until a month or two after the drug has been discontinued. A good rule in all valvular lesions is to include small doses of mercury in the interim tonics so frequently necessary in managing these cases. However, if the primary disease is luetic, once there has been a decided break in compensation little permanent improvement will follow the use of any of the antiluetic remedies. They should, nevertheless, always be diligently tried in the hope of producing a cessation of the process. Here even greater caution should be employed in the size of the initial dose. In the presence of edema, salvarsan should not be used.

ANEMIA.—Most of these patients are pale and frequently show a true secondary anemia. Iron and a tonic, particularly arsenic and mercury, as in the following prescription, are necessary from time to time:

R

Hydrargyri chloridi.....grain i (0.065 gram)
 Liquoris potassii arsenitis.....3 iss (5.85 c.c.)
 Tincturæ ferri chloridi.....3 iiss (13.6 c.c.)
 Acidi phosphorici diluti.....3 i (31.1 c.c.)
 Syrupi limonis.....q. s. ad 3 iv (124.40 c.c.)

Sig.: 3 i p.c. in water.

If this is not done these patients lose their "pep" and energy from time to time. The blood examination seldom reveals any satisfactory

results from the administration of such hematic tonics, but symptomatically the patient feels better. In some cases **Fowler's solution** alone is better borne.

The treatment of these minor symptoms will be discussed in detail under the treatment of individual symptoms. However, in patients presenting such minor symptoms, in spite of the fact that there is no direct or specific indication for the use of **digitalis**, small doses of the tincture, from 5 to 10 minims (0.3 to 0.60 gram) three times a day will, in addition to the other measures, often make the difference between success and failure in treatment. After the relief of these symptoms a general dietetic and hygienic future course must be planned.

Such patients should not take part in any activities which induce the slightest possible shortness of breath. It may be argued that it is only by exercise that physiological hypertrophy is induced, and this might have some foundation if there had been no evidence of deep muscular damage; but once symptoms have appeared, the ordinary duties of a quiet occupation furnish sufficient muscular stimulus for the average patient; for this reason, if the family has been living on the top floor of an apartment house, the ground floor, or at most one flight up, should be taken. Curiously enough cardiac patients seem to have a fondness for a top floor. In a private house the bedroom should not be more than one flight up.

ALTITUDE.—Such patients may usually safely go to an altitude of 2,000 feet. After 3,000 feet great precaution should be exercised and at the first onset of symptoms the patient must seek a lower level. As a rule individuals with cardiac involvement do better at the sea level, but not near the seashore.

MARRIAGE.—Unless there is marked evidence of decompensation, there is no contra-indication to marriage on the part of men, with the possible exception of those suffering from aortic regurgitation. The occasional occurrence of death during the sexual act in such patients should always be borne in mind.

In the case of women, marriage is contra-indicated only because of the danger resulting from pregnancy and labor. It is quite true that many women who suffer from minor symptoms associated with mitral regurgitation do have large families with little or no serious inconvenience, yet there is always considerable risk. The well-marked cases of mitral stenosis are, however, nearly always bad risks because of the likelihood of the occurrence of sudden pulmonary edema during pregnancy.

The chief points of value in estimating the likelihood of the heart being able to meet the demands of pregnancy are (1) the history or absence of the occurrence of a previous loss of compensation; (2) how the heart responds to the demands of ordinary life; (3) whether or not the patient has frequent infections and a disinclination for ordinary exercise; (4) whether there is a difference of more than ten beats in the pulse frequency when the patient is in the horizontal and upright

posture; (5) the relation of the urine output to the intake. Even if one points out these dangers it seldom prevents matrimony, either because pregnancy seems far off to the prospective bride or because she wishes some one to take care of her when the illness due to her heart attacks her. Practically marriage does add years to the life of many such women, who otherwise have been compelled to do hard work with no periods of rest, thus bringing on an early decompensation.

What should be one's attitude when pregnancy has taken place in a patient who presents some of the minor symptoms of broken compensation?

In general the outlook is infinitely better than the symptoms seem to warrant, and most patients pass through their pregnancy satisfactorily. If there has been a decided break in compensation nature usually produces a spontaneous abortion. In the first group mentioned one should wait until the sixth month of pregnancy, when, if there has been no decided loss of compensation, the patient should be kept under very close observation, mostly in bed, until the end of pregnancy. If at the sixth month unmistakable symptoms of failing compensation are in evidence—not the slight edema of the legs so common in most pregnant women, but a slight general anasarca and dyspnea—then the labor should be induced. At any time the onset of pulmonary edema demands active treatment, but labor should not be induced before the edema has subsided.

The use of **tobacco** should be **restricted**. It cannot be said that the use of a small amount is uniformly bad, but unquestionably excessive smoking in the subject of high pressure is often productive of harm; therefore the cardiac patient must be taught to look forward to the gradual elimination of the use of tobacco. It should be impressed upon him that he must visit the physician on a regular specified day every two or three months for reëxamination.

Outline of Treatment When Minor Symptoms Have Appeared

1. General directions as given in outline on p. 166.
2. Absolute rest in bed for at least three days. Relative rest for a few weeks thereafter. An extra hour of sleep each night for the rest of life.
3. Change of occupation if symptoms are due to overwork.
4. Life on level ground—avoidance of altitude above 3,000 feet.
5. In general, marriage to be avoided.
6. Restriction of tobacco and coffee.
7. Active treatment of cause of underlying lesion. Occasional courses of small doses of potassium iodid and mercury, in all cases in which there is a definite indication for its use, as well as in refractory cases, due to any cause.
8. Small doses of digitalis for two weeks to be repeated later.

9. Treatment of special symptoms:

- | | | |
|--|---|--|
| | { | Dry diet |
| | | Avoidance of foods producing flatulence, such as cabbage, beans, etc. |
| | | Fresh fruits |
| (a) Stomach | | Fats |
| | | Eggs |
| | { | Cheese |
| | | The home use of alkalis, and carminatives, such as bicarbonate of soda, peppermint, etc., on the first appearance of flatulence. |
| (b) Nervous symptoms and distressing sensations about the heart. | { | Bromids |
| | | Cratægus (Fluid extract, mxx [0.33 fluidram] t. i. d.) |
| | | Hoffman's anodyne |
| (c) Chest pain | { | Counterirritants |
| | | Iodids |
| | { | Nitrites |
| (d) Lungs | | Local treatment of nose and throat |
| | | Creosote |
| | { | Codein |

10. A course of Nauheim baths or any other safe treatment which forms an excuse for a regular vacation period.

11. After disappearance of symptoms patient to report to physician at least every two months for physical examination.

INDIVIDUAL SYMPTOMS AND THEIR TREATMENT

Among the early symptoms, *shortness of breath* is easily the most common. This is present only on moderate exertion, and is similar to that experienced by any one who carries out some unaccustomed exertion, except that it is more easily induced than is normally the case, and persists longer. It is essentially different from the dyspnea of the later stages of the disease, and is a valuable warning. It may be in the form of frequency of respiration (polypnea) or difficulty in breathing (dyspnea) or may appear only when the patient lies down, so that he is forced to sit up to breathe (orthopnea).

The only treatment lies in prevention, *i.e.*, the cultivating of the mental attitude that will act as an antidote to hurry, and to extra effort. Dyspnea, as well as most of the major symptoms, such as pain, cough, flatulence, etc., are worse if exercise of any kind is indulged in within half an hour after a meal.

When this shortness of breath becomes evident on slight exertion, small doses of *digitalis*, given for a few weeks, are of undoubted value, after which time the patient is apparently as well as ever. But recurrences will take place, and they are to be managed along the same general lines.

The dyspnea of the later stages is essentially different from that which appears before the break in compensation. Here the patient becomes dyspneic without any exertion, and at the most unlooked-for times. It is usually in the early morning hours that this symptom is most troublesome. He cannot sleep because of this dyspnea, or if he does fall asleep, awakes with a gasping; this is so disagreeable that he is afraid to go to sleep again, and this makes matters worse. At other times he becomes dyspneic during the day without appearing to notice it.

The Cheyne-Stokes phenomenon, either partial or complete, is present in the case of nearly all those who have high blood-pressure and in a large proportion of the others who have had a few breaks in compensation. It is frequently present for a year or more before death. This is especially so during sleep, and becomes noticeable only when observed during waking hours. Commonly the patient himself does not recognize it.

There is no specific treatment for this form of dyspnea. It is simply an index of the progress of the disease. When it becomes severe enough for the patient to appreciate it and suffer as a consequence of it, recovery is a rarity.

For individual attacks of dyspnea, **Hoffman's anodyne** in $\frac{1}{2}$ dram (1.95 c.c.) doses repeated every hour or so is often efficacious. It should be given in sugar and water.

However, it soon loses its effect, and the abnormal respiration continues in spite of digitalis. Then *morphin* is our only recourse. Generally it is necessary to give it hypodermically in order to obtain results.

In the administration of morphin there is much fear that the patient will forget to breathe or that the medullary center will not respond to the increase in carbon dioxide when it is benumbed by the narcotic. Of this there need be no fear. On the other hand the terror of the dyspnea and the sleeplessness which results will do much to still further break down the compensation, unless sleep is secured.

At times, **atropin**, grain $\frac{1}{100}$ (0.00065 gram) or larger doses at bedtime, by hypodermic, will control the attacks, and should be tried.

Dropsy.—**Rest in bed** is the best general measure for the treatment of this condition. Most of the early cardiac dropsies disappear when the patient remains in bed for three or four days, only to return when he gets up.

In those patients who insist upon getting about and who are suffering from a slight dropsy that is only noticeable at the end of the day, the application of a bandage in the morning—from the feet up to the knees—and the addition daily of an extra hour in bed, is a practical, temporary measure.

When the dropsy becomes severe, other measures must be employed in addition to rest in bed. Of these, **digitalis** easily takes first place.

Cardiac dropsy is the red light pointing to right heart-failure, and digitalis is always indicated in right heart-failure, no matter what the

cause may be. It has an especial predilection, however, for the right heart-failure consequent on rheumatic disease.

Sometimes the drug is not active until the abdominal cavity is relieved by paracentesis. At other times it is effective only after active purgation.

If no results are obtained in three days one should change the digitalis preparation employed. A **Niemeyer pill** given under these circumstances has often made the reputation of a consultant. One three times a day for not more than three days should be given. This should be a standing order, because these patients are easily salivated. A single dose of **calomel**, and 1 dram (1.95 grain) of compound **Jalap powder** is generally indicated at the beginning of treatment, but active continuous catharsis given with the idea of reducing edema is seldom well borne. In the few cases in which good results follow the purgation, the **Jalap powder** or **elaterin**, grain $\frac{1}{6}$ (0.0108 gram) repeated daily, are efficient. Commonly it will be found that after the first dose active catharsis does not avail much for the relief of dropsy. **Hot baths and hot packs** are of value when there is coincident renal disease, but one must be very careful during the administration of the first hot bath or pack, because some cardiac patients become very much cyanosed. If this does not happen it is likely that the baths are efficient for that individual. **Pilocarpin should under no circumstances be employed**, as it frequently produces pulmonary edema in cardiac patients.

Pulmonary Edema.—Pulmonary edema is a frequent symptom in the course of valvular disease. It is especially frequent in mitral disease. The treatment consists (1) in a hypodermic injection of **morphin sulphate**, grain $\frac{1}{3}$ (gram 0.0216), with **atropin sulphate**, grain $\frac{1}{75}$ (gram 0.000846), (2) **dry cups** applied to the base of the lungs, or in the absence of cups a large mustard plaster, (3) reassuring the patient that he will not perish. This statement is of inestimable value as an adjuvant in treatment. The friends should, however, be informed at once of the seriousness of the condition. Sometimes **nitroglycerin** is helpful, particularly if high blood-pressure is present. **Bleeding** is occasionally of service if cyanosis is very marked.

Cough and Bronchitis.—The earliest cough is a single effort cough. It is noticeable only on exertion, on going out in the cold or at the beginning of a sentence. It is frequently called a stomach cough because it often comes after a full meal. It is not troublesome and is only noticed by the friends of the patient.

Unless there is an added bronchitis, the cough itself rarely calls for treatment. Frequently it will be found that there are enlarged follicles in the pharynx—an enlarged lingual tonsil—or some congestion of the larynx. In such cases, local treatment with a 2 per cent. **AgNO₃** solution is often helpful.

When there is an associated bronchitis—particularly in old people—it is very resistant to treatment. Here the addition of small doses of from 2 to 5 minims (0.125 to 0.31 c.c.) of the tincture of **digitalis** to

each dose of the cough mixture, containing **creosote** or a **terebene** derivative, and **codein** or **heroin**, is of much value in hastening recovery. Of course if the attack is very severe, **rest in bed** is absolutely necessary. If there has been a previous severe break in compensation, such an attack of bronchitis should be considered just as serious as pneumonia occurring in a normal individual.

Failure to regard bronchitis with the slightest elevation of temperature as a serious lesion in a cardiac patient is responsible for a large proportion of the deaths in such patients.

Late in the course of broken compensation, the presence of cough, due to congestion of the bronchi and lungs, from back pressure, is a serious complication. Each attack of coughing is as depressing to the heart as would be the running up of a flight of stairs.

This cough must be suppressed at all hazard, and codein or morphin must be given in sufficient doses to accomplish this result. Usually, codein, grain $\frac{1}{4}$ (gram 0.0162), or heroin, grain $\frac{1}{12}$ (gram 0.0054) every three hours, is sufficient. Sometimes chloral in 5 to 10 grain (0.324 to 0.650 gram) doses in addition to the morphin is advised.

No preconceived fear as to pulmonary edema, etc., should cause the practitioner to withhold the narcotic.

Digestive Symptoms.—Almost all cardiac patients suffer sooner or later from symptoms referable to the digestive tract. Often these symptoms are treated for years on the assumption that they are due to disease of the stomach, and only a thorough examination reveals the real cause. The stomach may well be termed the red light signal station of all of the internal organs. The time of the appearance of these stomach symptoms may be divided into two periods: (1) before there is evidence of broken compensation, (2) during the period of broken compensation. In general the symptoms consist in the sense of fullness and oppression, coming on soon after meals, with belching, and later a sense of precordial distress, rarely of pain in the abdomen or chest. Frequently there is the complaint of pain radiating down the arm, particularly if exercise of any kind is indulged in after meals. Often it is not noticed until the patient goes out in the air.

In the first group, in the absence of evidence pointing to some other organ, it is sometimes difficult to decide whether the cardiac lesion is an accidental finding or is the causative factor.

It is wiser to record it as a causative agent and treat it along these lines. The treatment should be first **dietetic**. Cardiac patients, as a rule, do not bear fats well. Butter, cream, fats, cheese, must be greatly restricted, if not entirely eliminated. Fresh fruits, and indeed most fruit, with the possible exception of stewed prunes, should be interdicted. The same applies as to fruit junces, lemonade, etc. If there is no complaint of flatulence or gas, the fruits may be allowed. The same rule applies to buttermilk. In general a dry diet should be prescribed. The liquids are to be taken from one to two hours after meals. Soups are forbidden. Coffee and tea are best borne if cream is omitted. Some patients bear carbonated waters quite well and others react badly.

176 CHRONIC VALVULAR DISEASE OF THE HEART

At the first examination, if there has been a complaint of fullness and pain an hour or two after meals, an alkaline powder such as follows should be prescribed:

Natrii bicarbonatis 3 iv (15.50 grams)
 Magnesiae ustae 3 iii (11.65 grams)
 Caryophylli olei saccharati 3 ii (7.80 grams)
 Sig.: 3 i half an hour after meals.

The quantity of magnesia should be increased or decreased as the condition of the bowels requires.

In the cases in which the patient is attending to his occupation he should regulate the hours of his work and meals so that he may rest an hour after meals. In the event of his being unable to do this the mid-day meal should be a very light one, with some liquid nourishment in the middle of the morning and afternoon.

Most cardiac patients lose weight and consequently have ptosis of the abdominal organs, including the kidney, which further increases the difficulty in breathing, thus making for decreased ability to work. Such patients complain toward the end of the day of weakness, etc., and an all-gone sensation in the pit of the stomach, gas and flatulence, etc.

At the first examination, if there is the slightest possible evidence of ptosis, a three-inch-wide strip of adhesive plaster should be applied from the right lumbar region over the left hip, and two other similar strips added, one above and the other below the first. They are to be carried across the whole abdomen. This application gives a feeling of stability and support which is often quite surprising. Occasionally it is not well borne, and the patient should be instructed to remove it if that is the case. If relief follows this measure a belt may be ordered, but often two or three applications of the plaster, at intervals of two weeks, are sufficient to tide the patient over the attack.

Constipation is not a characteristic of cardiac disease, but is frequently present. It is often due to lack of exercise and to the diet. In *fat* cardiac patients, **salines** generally do good. Those which contain large amounts of sodium chlorid, such as Pluto water, should, in the presence of dropsy, be avoided.

Nervous patients bear salines *badly*. One of the **vegetable laxatives**, such as cascara, compound Jalap powder or licorice powder, is preferable. When the bowels move freely the patient feels better, but extreme purgation is a severe strain on the cardiac patient. For that reason many of them complain of exhaustion after an enema.

High colon **enemas** are frequently prescribed for patients suffering from high blood-pressure, and are often well borne and do much good, but if cardiac decompensation is present they should be given cautiously and discontinued on the appearance of prostration.

In the severer types of digestive symptoms—such as are met with

in bed, patients suffering from broken compensation—the sufferer often feels better for half an hour or more after each meal, in which case he should be fed often and in smaller quantities. When eructations relieve the cardiac distress the patient is of the impression that the gas is the whole cause of the trouble, and that if this could only be relieved good health would return.

Undoubtedly gaseous distention of the stomach does embarrass the heart, but this flatulence frequently depends upon a central cause rather than upon the local condition of the stomach.

Death follows such belching and gastric distress is described as being due to acute indigestion, but this is not the case. Frequently this belching is promptly relieved at the time of the use of **Hoffman's anodyne**, in $\frac{1}{2}$ dram (1.95 c.c.) doses, repeated as required, in other cases by the use of the following:

Chloroformi spiriti $\frac{3}{4}$ i (3.696 c.c.)
 Ammonii spiriti aromatici $\frac{3}{4}$ iii (11.088 c.c.)
 Tincturæ lavendulæ compositæq. s. ad $\frac{3}{4}$ ii (60 c.c.)
 Sig.: $\frac{3}{4}$ i (3.696 c.c.) every two hours.

Other carminatives, such as cloves, ginger, and peppermint, must be tried from time to time.

Acute dilatation of the stomach is not infrequent, and is a serious problem. In such cases there is repeated belching, swallowing of air, vomiting of small amounts of dark-colored material, much fullness and distention of the abdomen, and oppressive dyspnea. The patient cannot lie down nor remain in one position for more than a few moments, and his distress is extreme.

If Hoffman's anodyne and the alkalis do not give relief the practitioner's next thought is to resort to **morphin**, but he will often be disappointed because after two or three injections no relief is obtained.

This is one of the very few cardiac complications which are not relieved by morphin. Under no circumstances should the doctor leave such a patient until he is relieved. The best remedy is the **stomach tube and lavage**. This suggestion appalls most physicians, who fear that the straining of the patient while swallowing the tube will be sufficient to produce unfavorable or fatal results. However, as a matter of fact, there is no danger and after the procedure is finished the patient is usually relieved and goes to sleep. It is a sovereign remedy, and many patients die because it is not employed. The Rehfuß or any other duodenal tube is easily swallowed and is a great improvement for this symptom. It may be left in for an hour or more. When the symptom is very severe, pituitrin 2 c.c. [32.4 minims] (obstetrical) given hypodermically every two hours is of service. Abdominal massage is often of some help.

Vomiting.—Occasional vomiting is fairly frequent, and demands no treatment except starvation for a day or two, and **regulation of diet**.
 VOL. VI.—12.

When it is persistent, medicines administered for the disease such as digitalis, etc., should be considered as the most likely cause. After the discontinuance of the medicines, gastric sedatives such as **bismuth**, or **cerium oxalate** should be employed. The following prescription is often efficient:

Bismuthi subnitratissgrains viii (0.52 gram)
 Natrii bicarbonatisgrains v (0.324 gram)
 Hydrargyri chloridi mitigrain 1/6 (0.0108 gram)
 One powder every three hours for four doses.

Ice is seldom of avail and often increases the flatulence which is so commonly already present; absolute starvation for a day is frequently necessary. If these measures fail, or if there is evidence of a chronic gastric catarrh, tincturæ capsici, 1 minim (gram 1/16) before meals in a wine-glass full of water may be given.

If all of these measures fail, the stomach-tube should be fearlessly employed, because if this vomiting is not stopped promptly it is apt to have a fatal ending.

Hiccough.—Hiccough is a very distressing symptom. It is usually manifest only in advanced cases, and in itself aggravates the patient's condition. It is very difficult to control, and if it is long continued recovery is uncommon. The ordinary household maneuvers should be employed, such as holding the breath, taking long breaths, etc. A measure sometimes of service is placing a spoon on the tongue and depressing it so as to push the tongue far back in the throat, and holding it there. The stomach is responsible for a fair percentage of these cases, and through this the reflex of the phrenic is disturbed. The patient should be starved for twelve hours, no liquids being allowed. From time to time **aromatic spirits of ammonia** and **Hoffman's anodyne** should be given. These failing, a **mustard-plaster** over the epigastrium may afford relief. Sometimes taking a food or medicine which is strong, bitter or sharp in taste stops the paroxysms. **Benzyl benzoate**, 1/2 dram (1.9 c.c.) of a 20 per cent. solution or emulsion repeated every three hours frequently is efficient. It has no toxic effects.

Finally, when they are long continued, rest must be obtained by the use of **morphin**, although frequently it does not prevent the occurrence of the hiccough during sleep. One must keep on trying one remedy after another, inasmuch as in all hiccoughs the psychic effect of a new remedy is always a powerful adjuvant. The author has not been able to convince himself that any of the remedies directed toward influencing the phrenic nerve itself have been specifically efficacious.

Insomnia.—Sleeplessness is one of the earliest of the minor symptoms to appear. The patient seldom complains greatly of it, because of the insidious onset. It is the worst of the minor symptoms because it is constantly wearing out the patient's reserve power. More than any other symptom, with the possible exception of pain, it must be overcome.

This applies in all stages throughout the life of the cardiac patient. In these early cases a glass of hot milk or cocoa is sometimes sufficient to induce sleep; in others, hot rum or a bottle of beer is sufficient, but in nearly all instances this habit of sleeplessness—for this it soon becomes—cannot be broken except by the use of drugs. In the early cases, **sodium** or **potassium bromid** in 20 grain (1.30 gram) doses three times a day and at bedtime for three days, and after that at supper and bedtime, is often sufficient to bring about natural sleep. There is no special value in the mixed bromids. In other cases, **chloral** in 15 grain (0.972 gram) doses after supper and at bedtime is necessary. The **elixir** of **chloralimid** in $\frac{3}{4}$ ss doses at bedtime is safer and generally efficacious. In the more advanced cases, **veronal** in 10 grain (0.65 gram) doses in hot milk, repeated in three hours if needed, is efficacious. **Luminal**, in from 3 to 5 grain (0.195 to 0.324 gram) doses, is sometimes more successful than veronal. If the major symptoms are present, it is usually necessary to resort to **morphin** in order to secure a few nights' sleep, as these milder agents are now inefficient. For the first few nights it should be given in doses of $\frac{1}{6}$ to $\frac{1}{4}$ grain (0.0108 to 0.0162 gram) hypodermically. Its action by mouth is slow and not nearly so satisfactory. If no effect follows within half an hour after the hypodermic, it may be repeated. The oral administration of the narcotic should not be repeated within two hours.

Headache.—Headache is frequently temporal, occasionally frontal. When due to intercurrent causes, such as eye-strain, constipation, etc., it should be treated on the basis of the intercurrent cause. When it can be attributed to the cardiac disease, **rest** is of immediate importance. A powder containing **phenacetin**, grains 5 (0.324 gram), or **aspirin**, grains 10 (0.65 gram), with or without **guarana**, 5 grains (0.324 gram), is a safe and satisfactory agent. The author does not find that the average cardiac patient is any more prone to cyanosis and cardiac distress after moderate use of these remedies than is any other class of patients.

There are always some people who are susceptible to the coal-tar derivatives; but the condition of the heart, as far as we can find on gross examinations, has little to do with this idiosyncrasy. The cyanosis is often a question of blood chemistry rather than of cardiac insufficiency.

When the headache is frequent and continuous a treatment of the cause underlying the cardiac lesion by **digitalis**, **iodid** or **nitrite** is commonly satisfactory. In cases associated with high blood-pressure, **bromids** are often of value. In the severer cases, **venesection** (a pint of blood being withdrawn) frequently relieves the headache for several months. This failing, absolute rest in bed should be insisted upon. One should try these measures in their successive order, and if they fail **morphin** is an unfailing source of temporary relief. Lumbar puncture may be employed as a last resort, but it is occasionally dangerous.

Delirium.—The delirium and mental aberration that is present in most cardiac patients during a severe loss in compensation is the cause of much alarm to the friends of the patient. While it always has a serious portent, yet, in the absence of other signs of progressive disease, it is not necessarily fatal. When it continues for several days the question is frequently asked: Will the patient be permanently insane?

In general a positive statement can be made as to such an outcome. It is very rare that these patients actually become insane. Here again one must closely distinguish between an insane person who has a cardiac lesion and one who is suffering from the delirium of decompensation.

As to the cause of these mental changes—the laity almost always believe it to be due to the medicine prescribed, particularly if morphin has been given hypodermically. On the other hand, many physicians believe that digitalis is responsible for the delirium.

Except in the rarest instances neither of these views is correct. It is an unquestioned fact that digitalis has, in very exceptional instances, when given in very large doses, produced this phenomenon. But this is exceedingly rare. The same holds good to a lesser degree as to morphin, whereas delirium is a common phenomenon in all cardiac patients.

When there is much adverse criticism it is a good practice to stop all medicines for a day or two unless there is dire necessity for their use. The continuance of the symptoms will be convincing. Of course the symptoms stop at times of themselves, but usually they return.

As to the treatment: A **hot pack** is frequently serviceable. **Bromids** are useless. **Paraldehyd** in 1 dram (3.75 grain) doses is a safe agent. At times it may be increased to 2 drams (7.80 grams) every three hours. **Chloral** in from 15 to 20 grain (0.97 to 1.30 gram) doses is a valuable agent and is practically devoid of danger within these dose limits. **Veronal** in 10 grains (0.65 gram) doses is safe but is not as reliable as it is in delirium due to other diseases. **Luminal** is more often serviceable, and is given in doses of from 3 to 5 grains (0.195 to 0.324 gram). Occasionally it produces a severe urticaria.

Cardiac Pains.—Pain in the region of the heart is so frequently due to causes other than the heart, that it has become almost an axiom that in the presence of precordial pain, the heart is the last place in which to look for the cause. Yet this is only relatively true. Most cardiac patients do have pain about the heart at some time. One must distinguish between discomfort and a sense of weight and actual pain. If the pain is continuous, and there are other evidences of cardiac disease, the cause is almost certainly in the heart, whereas if it is paroxysmal and no cardiovascular symptoms are evident, the cause is likely to be found elsewhere.

Where the disease involves the base, it involves the reflex arcs of the cervical and thoracic nerves. In the great majority of cases the pain is referred under the left breast and across the mid-chest. It com-

monly radiates down the inner side of the arm to the little finger. Often hyperalgesia is also present.

Other thoracic pains are due to pulmonary infarct, pleurisy and pericarditis.

Pain in the epigastrium in cardiacs is usually due (1) to dilatation of the right heart, (2) to congestion of the portal system, and (3) to enlargement of the liver. Nearly all decompensating cardiac patients have pain, tenderness or uneasiness in the epigastrium. The relief of this pain follows in proportion to the relief of its cause. It is seldom agonizing, but is constant and annoying.

LOCAL TREATMENT.—By the use of counterirritants over the heart the pain can frequently be relieved. MacKenzie has pointed out that this is equivalent to blocking the nerve impulses of pain, which are referred from the spinal centers. The disturbed function of the heart itself is only manifest through the reflex spinal arc, because the nerves from the heart do not convey painful sensations. By blocking anywhere along this arc, painful impressions are inhibited just as they would be blocked by a cocain injection. This definitely explains the mechanism by which counterirritants relieve pain in a deep organ, such as the heart, through treatment directed at a considerable distance from the diseased viscus. For quick results a **mustard plaster** is the best and handiest of these local pain-relieving agents. A few drops of **chloroform** in the palm of the physician's hand, then quickly applied and pressed over the painful region, and kept there despite the patient's protests, until there is a burning sensation felt between the physician's fingers, is a rapid and most efficient way of producing this counterirritation and consequent nerve-blocking. Any of the popular liniments will accomplish this result, but less effectively than the mustard. If the blocking is to be continued, the counterirritation must of course be kept up. In such cases, repeated applications of **iodin** or some other substance to produce blistering will usually be necessary. Sometimes a strapping of **adhesive plaster** keeps the chest quiet and so relieves the pain about the heart. This is the mechanism of the relief which sometimes follows the use of porous or belladonna plasters. For quick action, therefore, one can first use a counterirritant locally and Hoffman's anodyne internally.

For the distressing sensations about the heart, particularly the uncomfortable feeling about the apex, the smothering sensations, and the consciousness of a powerful extra-systole, **Crataegus** has been found to be more satisfactory than any other agent for continuous use, although it often fails, as do all other remedies, which must be given blindly without any definite physiological indication. It is not a quickly acting remedy but must be given over long periods. In the author's experience it has been more successful in the aortic cases than in the mitral ones. The dosage is 20 minims (1.35 c. c.) t. i. d. of a good fluid extract or its equivalent. Much care should be exercised in securing an efficient preparation. It may be given for months at a time and does not have any deleterious effect upon the stomach. Its effect may often be enhanced

by temporarily combining 20 grains (1.30 gram) of bromid with each dose, for a few days.

Iodid.—For the relief of constant pains in the chest, especially those associated with aortic disease and referable to the sternum, the **iodid of potassium** is of unquestioned value. It is immaterial whether the cause is lues or arteriosclerosis. However, cases of rheumatic origin are less certainly relieved. As to just how the iodid accomplishes this, is not known. Usually 5 grains (0.324 gram) of potassium iodid t. i. d. are sufficient.

SEVERE CARDIAC PAIN AND DISTRESS.—When the pain is very severe, nothing short of **morphin** in full doses, grain $\frac{1}{3}$ to grain $\frac{1}{2}$ (gram 0.0216 to gram 0.0324), will suffice to give relief. This is especially true if there is an accompanying dyspnea. If there is no decided result from the first hypodermic of morphin in any cardiac case within half an hour, then, before giving another dose, one should warn the patient's friends that this is likely to be a serious attack. Patients who require more than $\frac{1}{2}$ grain of morphin to relieve the pain are always in a dangerous condition and often die within a short time. The friends are often only too anxious to ascribe the fatal ending to the repeated use of the hypodermic medication. Of course, morphin does not kill by reason of any cardiac effect, and it should not be withheld, but the practitioner should always protect himself in such events by foretelling that it is the disease, and not the hypodermic medication. The practitioner should not leave the patient if the pain is not relieved by these doses.

Cramps in the Legs.—For the severe cramps in the legs with aortic disease which awakens so many patients in the middle of the night, the use of thick **woolen stockings** up to the knee is often sufficient. The cause of this pain is probably analogous to the oppression and pain in the chest experienced by these patients on going out into the cold. About 3 a. m. the temperature of the room usually falls, and this may account for the appearance of the pain at that time. When it is not prevented by the warm stockings, placing the limbs in hot water during the attack may afford relief. In other cases it is necessary to administer from 0.31 to 0.625 grain (5 to 10 minims) tincture of **opium** at bed-time each night, to prevent such attacks. The danger of contracting the opium habit is *nil* in the case of any cardiac patient who has reached this stage.

Buzzing and Noises in the Ear (Sensation of hearing the heart-beat in the ear, dizziness, etc.)—All of these symptoms occur in cardiac patients but in almost all instances they are associated with some middle or internal ear lesion, which becomes noticeable to the patient only when compensation begins to fail. Hence, treatment devoted to the ear is of the first importance, and when a patient with cardiac disease complains of any of this group of symptoms, the ear must be considered as the primary cause until proven otherwise.

Bromids in 20 grain (1.30 gram) doses, three times a day, give more subjective relief than does any other medicinal agent.

Fainting Spells.—Fainting spells may occur in any form of valvular disease.

Aromatic Spirits of Ammonia internally, and smelling salts externally, and, most important, the **recumbent position**, are usually sufficient to bring relief.

Sometimes the patient uses the euphonious title "fainting spells" to denote true epileptic convulsions.

Bad Taste and Bad Breath.—These minor symptoms are seldom complained of unless the patient is asked specifically as to their presence. One or the other is quite commonly present during a break in compensation. Sometimes the sense of bad taste antedates the onset of other symptoms by a considerable period of time. There is nothing characteristic about this taste, but it is usually described as flat or bitter. Active catharsis by **calomel**, and diuresis obtained either by **digitalis** or **diuretin** in small doses, commonly gives relief. Many of these patients have a muddy complexion which suggests the old-fashioned term,—biliousness. There is a coated tongue and loss of appetite. In such cases foods containing eggs, butter, cream, milk, cheese, and fat should be rigidly eliminated from the diet, because no matter how the fact may be explained these foods do aggravate the symptoms. The frequent use of calomel, supplemented by the daily administration of bile-salts, accomplishes a fair measure of success in this group of cases. Of course, one must inspect the tonsillary crypts as putrefaction here is sometimes responsible.

Excessive Perspiration.—This is a common complaint in the stage of decompensation. It is sometimes Nature's method of sparing the kidneys, and as such should be welcomed. At times it seems to bear a definite relation to the dyspnea. When the dyspnea is not urgent, the sweating is profuse, and *vice versa*. In health, in the lower animals particularly, this phenomenon is common. A dog does not perspire on a hot day, but on the other hand breathes rapidly. In the cases associated with diminished kidney excretion **diuretin** often affords relief. In most cases **atropin** gives relief for a few days, but soon loses its effect. A **vinegar sponge bath** at bedtime is sometimes efficacious. Weakness is a comparatively early symptom in all cardiacs, and rest is the best cure. It is then a "late in the day" symptom. In the period of broken compensation it is frequently a distressing morning symptom. The depression, both mental and physical, is extreme in the early morning hours. **Alcohol** in one form or another is often of great service. In fact, it is of service in some patients throughout the day. When this depression is extreme, **opiates** constitute the sheet anchor of treatment.

BROKEN COMPENSATION

Sooner or later, in nearly all cases of valvular disease, the major symptoms are in evidence. Frequently the process is a gradual one, following the advent of the minor symptoms or occurring because of an intercurrent infection which causes the muscle to give out quickly. This failure of the muscle can finally be predicted in any case of valvular disease, inasmuch as a lesion of either valve or muscle presupposes a coincident infection of the other. Once there is a break in compensation

in general, the treatment must be the same, no matter what the particular lesion may be. Technically it is usually the treatment of tricuspid regurgitation—the final lesion in nearly all cases of broken compensation. Practically it consists in: (1) the treatment of the heart itself, (2) relieving congestion and disorders of physiology of other organs. Often the relief of these latter is more important than that of the heart, and once they are functioning normally the heart can take care of itself. Here again absolute rest is easily the most important of all remedial measures. There is now little trouble in securing the patient's consent to rest, but it is difficult to make him remain constantly in bed. One must enlist his coöperation; otherwise as soon as the physician leaves the house he will attempt to get out of bed. If the reason for his absolute rest is conveyed to him in language that is intelligible, obedience can usually be obtained. A word-picture such as the following is often successful: A cut or injured finger which is in constant motion fails to heal, yet on being bandaged and kept quiet and free from irritation it heals promptly in a few days. While the patient is lying on his back the heart normally beats 60 times a minute, while he is sitting up it beats 80 times, and while he is standing and walking, from 110 to 120 times; therefore, there is a difference between lying flat and walking of between 40 and 50 beats for every minute of every hour of the day that the patient is up and about. The heart has no possible chance for rest and recuperation, unless the patient lies constantly in the horizontal position.

In prescribing rest the physician must give positive and clear directions. Rest in bed must be absolute; if possible the patient is to remain on his back, or if dyspnea is marked, he may sit up in bed; he must use the bedpan and may not go to the table for meals. He should not be allowed to read the paper for the first three or four days, nor to see any visitors except his immediate family. A nurse should be employed at once, and she should be on duty at night during the first week of treatment, otherwise the patient will try to help himself when he needs attention. Of course any one who cannot use the bedpan should be allowed to use a commode in preference to catheterization, but cardiac patients usually learn to use the bedpan. Many patients cannot lie down, because of dyspnea, and as a consequence they strenuously object to lying in bed unless they can have their feet on the floor. When this feeling of distress cannot be alleviated the patient's wishes in this matter must be granted. Sometimes lying in a Morris chair solves the problem. Occasionally sleep can only be obtained while the patient is sitting up in a chair with his head bent forward on a pillow placed on a broad sheet supported on the arms of the chair. When this is the case this position must be allowed, but as far as possible the limbs should be kept in a horizontal position.

Diet.—The diet should be as dry as possible; certainly solids and liquids should not be partaken of at the same meal. If the patient is hungry one may usually allow dry toast, creamed potatoes, cereals, milk,

malted milk, tea, coffee, ginger ale, chicken, or lamb chop, the total amount of fluid in twenty-four hours not to exceed 32 ounces (946 c.c.). As a rule the patient is not hungry, but is quite thirsty. Here again one secures his coöperation by explaining the necessity of restricting the amount of fluid intake so that it may be compared with the output, the urine being measured during each twenty-four hours. The urinary output is generally a good index of the progress of the case. Salt must be interdicted because it increases the thirst, and if there is any concomitant parenchymatous nephritis it increases the edema. Therefore, it is a good rule, in the presence of edema, always to restrict the use of salt in the food. In the absence of edema it is sufficient to take the salt-cellar from the tray or table. If the digestion is good, fruits may be allowed; otherwise, the restriction should be similar to those already described under the dietary management of the minor digestive disorders. Fats, butter, cheese, etc., should be eliminated.

Hope.—All cardiac patients suffering from any of the minor, and particularly any of the major symptoms of decompensation, should be given as much hope and encouragement as possible. No matter how bad the case may seem to be, immediate recovery is always possible, even though permanent recovery may be impossible. A positive reassurance must be given repeatedly, even though there is no question on the part of the patient as to how he is progressing. It is one of the best of medicines and yet is most begrudgingly given. It is surprising what a beneficial effect hopeful announcements have on the cardiac patient. One might well argue that it can have no permanent physical effect, yet momentary effects in individuals suffering from cardiac involvement often mean months of life. One sees this frequently following the use of nitroglycerin. The symptoms are severe, and death may seem imminent. The relief afforded by the nitrite cannot possibly last in itself more than thirty minutes, yet such patients may live for months and years as a result of such a short physiologic effect. Hope is just such a remedy.

This hopefulness is a very large factor in the good results which are undoubtedly obtained from all of the so-called cures. The patient is repeatedly told that he is better and that recovery will certainly follow. There may be very rare cases in which brutal frankness is better, but it is very difficult, well-nigh impossible, for anyone to say truthfully to a cardiac patient that there is no hope.

Digitalis.—A very large number of cases of broken compensation in valvular disease will react to absolute rest alone, if it is sufficiently prolonged and thoroughly carried out. We have in digitalis, however, a drug of specific value in some forms of cardiac disease and which is useful in the case of all patients suffering from decompensation, no matter what the cause may be. In many cases of decompensation, no matter what the apparent contraindications to its use may be, every maneuver should be employed in an endeavor to give the patient the advantage of its use. When digitalis begins to act, there is an increase

of the urine output, a lessening of dyspnea, and of the minor symptoms. If fibrillation is present, the weaker, ventricular contractions which do not reach the wrist are gradually eliminated, and the pulse-beat approximates the apex-beat in frequency. The drug should be continued more or less throughout the life of the patient suffering from fibrillation.

ADMINISTRATION.—In general the effect of digitalis is to be measured by the amount of digitoxin contained in the preparation. The method of standardization depends upon the reaction of the heart of the frog or the cat to the drug. By the frog unit, which is the one in general use, is meant the amount of digitalis preparation, whether powder or liquid, which causes the arrest of the heart of a frog (of from 30 to 40 grams weight) in systole within thirty minutes. One gram (15.43 grains) of an ordinary good preparation of digitalis in powder form equals 50 frog units; therefore, 0.1 gram (grains 1.543) of such a powder equals 5 frog units. In general 20 frog units in a day is a fair dose. Of late the cat unit has been substituted by many pharmacologists. In any event the equivalent in cat or frog units of each preparation, whether it is a new proprietary or an old galenical, should be known before it is accepted for use.

The method of Eggleston, otherwise known as the body-weight method, is growing in popularity. This is especially true in hospital practice. It is founded on the principle of full digitalization within from ten to twenty hours after the beginning of the administration of the drug. The total amount is expressed in terms of the activity of the drug and of the patient's body weight in pounds. The cat unit is the standard employed. This is the quantity of the dry drug in milligrams which is required to kill one kilogram of cat when given slowly and continuously by the intravenous method (Hatcher). The average requirement for a man is 9.15 cat units for each pound of body weight. A cat unit is equivalent to 100 mgs. (1.54 grains) of an ordinarily good tincture. For an ordinary patient weighing 150 pounds, about 20 c. c. (5.42 fluidrams) of a good tincture is necessary. For accuracy any one of the following formulæ of Eggleston may be employed:

Formula I:
$$\frac{C. U. \times 0.15 \times W}{1,000} = \text{Grams of powdered leaf in total amount.}$$

Formula II:
$$\frac{C. U. \times 0.15 \times W}{100} = \text{Cubic centimeters of tincture in total amount.}$$

Formula III:
$$\frac{C. U.}{100 \times W} = \text{Cubic centimeters of infusion in total amount.}$$

In these formulæ, C. U. is the number of milligrams in one cat unit, and W. is the patient's body weight in pounds. The following example

illustrates the use of these formulæ: A patient weighs 150 pounds, and the digitalis available has an activity of 100 mg. to the cat unit. Applying Formula I for the powdered leaf, we have $100 \times 0.15 = 15$; $15 \times 150 = 2,250$; $2,250 \div 1,000 = 2.25$ grams of leaf in total amount. Applying Formula II for the tincture, we have $100 \times 0.15 = 15$; $15 \times 150 = 2,250$; $2,250 \div 100 = 22.5$ c.c. of tincture in the total amount. Formula III gives $100 \div 100 = 1$; $1 \times 150 = 150$ c. c. of the infusion in the total amount.

ADMINISTRATION OF AVERAGE CALCULATED TOTAL AMOUNT.—When the patient has received no digitalis within the preceding ten days, and the case is urgent from one-third to one-half of the total calculated amount is administered at the first dose. After an interval of six hours, from one-fifth to one-quarter of the total is administered. After a second six hours, from one-eighth to one-sixth of the total amount is administered. Thereafter, if more digitalis is needed, about one-tenth of the total amount may be repeated every six hours until maximal digitalization is secured. In the case of the example given above with the total amount being 22.5 c. c. (6.09 fluidrams) of tincture, the first dose would be from 7 to 11 c. c. (1.89 to 2.98 fluidrams), the second from 4 to 5 c. c. (1.08 to 1.35 fluidrams), the third from 2.5 to 3.5 c. c. (33.2 to 49.0 minims) and thereafter about 2 c. c. (32.4 minims) every six hours if required.

When digitalis is given by this method, its effects begin to become evident on the electrocardiogram within four hours and reach the maximum within another four hours and continue thus for twenty-four hours. The rate of excretion of digitalis following such dosage amounts to approximately 20 minims (1.25 c. c.) per day so that the effect of this dosage lasts for four or five days; after this it is necessary to give from 20 to 30 minims (1.25 to 1.90 c. c.) twice daily. When the method is used in private practice, the patient should be carefully observed for the first two days at least; it is indicated in severe attacks of decompensation especially if there is any objection to the use of opium. However, the average physician does not feel that it is safe to use these large doses in private practice; furthermore, the necessity for rapid digitalization is rarely necessary in private practice. Ordinarily 20 minims (1.25 c. c.) of the tincture four times a day is a sufficient dose. The best preparations, containing the largest amount of digitoxin are those obtained from the English leaves. Allen's English leaves have a world-wide reputation. The powdered leaf is quite the most efficient of the digitalis preparations. If the irritating effect on the stomach produces nausea, it may be given in capsules. Furthermore, many patients have digestive disturbances from alcoholic solutions of medicines of any kind. However, most practitioners prefer to use the tincture. In passing, it may be mentioned that one should specify the druggist who is to fill the digitalis prescription, or the pharmaceutical firm that manufactures it, because the average drug-store tincture of digitalis

varies as much as 50 per cent. in strength. The tincture may be conveniently prescribed in combination with elixir adjuvans as follows:

R

Tinctura digitalis.....3vi (22.50 c.c.)

Elixir adjuvans.....q. s. ad 3ii (59.20 c.c.)

Sig.: 3i (3.75 c. c.), t. i. d., p. c.

This obviates the necessity of accurate measurement of the dosage at each administration. It insures accuracy and obviates some of the disagreeable taste and odor of the drug. Any other menstruum which does not precipitate the digitalis may be used. The powder may be given in wafer or in capsule form. When digitalis is administered over long periods of time, a dose of calomel or blue mass given once a week adds to its efficiency. The infusion of digitalis has a widespread reputation, in that it is of particularly great value in the cardiac dropsies. Some of this good effect is due, doubtless, to the relatively large doses of digitoxin which the patients receive in the usual dose ($\frac{1}{2}$ oz. [15 c. c.]), rather than to the former belief that the digitonin keeps in suspension some of the active principles not largely contained in the tincture.

The fluid extract of digitalis in tablet form is a convenient way of treating the minor symptoms of ambulant cardiac patients but it is not nearly so reliable as the other preparations. It may be given in tablets containing 2 minims (gram 0.12) three times a day. In producing digitalization by any method, one should give the drug until physiological effects are obtained. These physiological effects are nausea, vomiting, diarrhea, extrasystoles not previously present, and the presence in the pulse of coupled beats; when any or all of these phenomena occur, the drug should be discontinued for a few days and then begun again at one-half the former dose. It must be kept in mind that the effect of digitalis on the stomach is a twofold one. On the one hand, there is the early local, irritating effect, as well as the nauseating taste, and these account for some of the gastric symptoms. On the other hand, the central effect is a later phenomenon and signifies a saturation for that individual. This later phenomenon will occur with any preparation of digitalis which exerts a sufficient physiologic effect to make its use worth while. There is no known way to obviate these central symptoms when the full physiologic action has been obtained. However, some preparations do not have the same local effect on the stomach that others do, and, consequently, have a wider range of usefulness.

OTHER PREPARATIONS OF DIGITALIS.—The French granules of Nativelle are made up largely of **digitoxin**; they are an efficient preparation and are always reliable. When the stomach will not bear medicines of any kind it is better to resort to hypodermic medication. For this purpose the **digitalin** so much used in the past is generally inefficient. If it is used, it should be given in large doses, grain 1/50 (gram 0.00132). The newer preparations such as **digalen**, **digipuratum** and **digifolin** are much more elegant and efficacious. It is sometimes possible to administer digitalis in the form of an alkaline solution of digipuratum by

rectum, but it is unreliable. The old-fashioned digitalis poultice applied to the kidney did not, of course, produce the digitalis effect. Within the last few years, a number of new preparations of digitalis have come into use.

Digalen.—Of these preparations just referred to, the most commonly used is digalen, said to be a solution of digitoxin, but believed by other pharmacologists to consist largely of digitalein. It is unquestionable that this does not disturb digestion to the same extent as the tincture, but the author does not feel that he has often witnessed decided beneficial results from its administration by mouth, even when large doses were employed. It is, however, a convenient form for hypodermic use. It has been stated that it is more than ten times as expensive, unit for unit, as the tincture. There is no question but that the physiological results follow its use when given intravenously, and in emergencies, it is the form most generally applicable. The dose in any case should be at least 20 minims (1.25 c. c.).

Digipuratum.—This is a preparation of the leaves from which much of the irritative material, including **digitonin**, which locally irritates the stomach, has been removed. Of course, the action of the digitalis on the digestive tract remains so that digestive symptoms following its administration are not entirely lacking. It is obtainable in two forms, the tablets containing 0.1 gram (grain 1.543) and a liquid containing 1 c. c. (1 gram = 15½ grains) digitalis leaves, or 8 frog units. Usually 12 tablets are necessary to produce an efficient digitalis effect; one tablet four or five times daily is the usual dose. Hypodermically, the dose is the same as by the mouth. When given intravenously for an emergency, one dose of 2 c. c. (32.4 minims) is usually sufficient. Similar preparations on the market under the name of **digifolin** and **digipoten**, are now in general use. The results are similar to those of the digipuratum.

SUBSTITUTES FOR DIGITALIS.—Nearly always when digitalis fails the substitute also fails, but one must, figuratively speaking, follow the example of the drowning man, and grasp even at a straw. Of these straws **strophanthus** is the one most commonly employed. Theoretically, it is an ideal preparation. In practice, it usually fails. The fact that it has no unpleasant taste often leads physicians to prescribe it in place of digitalis. If the true physiologic digitalis effect is obtained, the central effects are just as irritating as are any of the digitalis-like bodies. The dosage which produces physiologic effects, and the poisonous dose, are so close that it is much feared by laboratory workers. Generally 5 minims (0.3 c. c.) of the tincture three times a day is a sufficiently high dosage. **Strophanthin** is given intravenously. It is obtainable in ampules containing one milligram (1/64 grain), the equivalent of 15 frog units. The effect is very prompt. Because of its toxicity, the drug should be reserved for acute attacks of decompensation, when there is immediate danger to life. It should not be repeated nor used if much digitalis has recently been administered nor should a large dose be repeated within twenty-four hours. Occasionally death follows its use, but it is generally difficult to determine whether the patient would not have died anyway.

INDICATIONS FOR THE USE OF DIGITALIS.—Digitalis is, of course, specific only for those who suffer from auricular fibrillation, because of its effect in blocking the impulses which pass through the bundle of His. However, it is of inestimable value in other diseased conditions and, particularly, in right heart-failure. It is more effective in heart-failure due to rheumatic fever than when it is due to other causes. As to its use in aortic regurgitation, theoretically, it should not be used in the compensated cases, and practically, it is not well borne in these cases, except in small doses, unless the aortic regurgitation is due to rheumatic endocarditis. However, when a right heart-failure is associated with aortic regurgitation, as evidenced by dropsy, etc., digitalis should be given with just as free a hand as in any other form of right heart-failure; except in the presence of these symptoms, it is not well borne. In some cases of primary mitral stenosis in which symptoms are present and yet there is no enlargement of the heart, the drug is not well borne. In regular hearts the result is not so gratifying as it is in fibrillating hearts. The heart-beat is slightly slower, diastole is lengthened and the contraction of the ventricle is strengthened.

Contrary to what was formerly believed, the drug is frequently indicated in the decompensation of many patients suffering from high blood-pressure. This is especially true if there are evidences of stasis or any other signs of cardiac failure. In any such case, no matter what the apparent physiological contraindications may be, digitalis should be tried. Many patients who appear to be ideal subjects for the use of a nitrite react to digitalis and to nothing else. It is also indicated in cardiac insufficiency associated with a renal involvement. It is entirely useless in many of the functional disturbances, such as palpitation, extrasystole, tachycardia, etc. In fact it commonly makes these patients feel worse. Finally, there should be no hesitancy in the use of this drug in moderate dosage in any case of decompensated organic heart disease at any time, provided there are no digestive disturbances. It is a drug, the efficiency of which does not wear off. It is just as efficient after long use as after short use; its effect on the heart, all other things being equal, is the same one year as another. It should be given in small doses in the early minor disturbances of the cardiac patient. Often it renders possible the use of other remedies employed for the relief of these minor symptoms, when without its use nothing could be accomplished: this is especially true in the treatment of the winter bronchial attacks of cardiac patients whose hearts are apparently compensating.

CONTRAINDICATIONS TO THE USE OF DIGITALIS.—Indications to cease the use of digitalis are: (1) those referable to the heart and circulation; and (2) those referable to its effects on other organs. Among those referable to the heart itself are: (a) a marked grade of sinus arrhythmia that is independent of the respiration and is phasic in type; (b) premature contractions when not previously present, especially in the form of *pulsus bigeminus*, the "coupling of beats at the wrist" as discussed by the older writers (this is particularly noticeable on sitting

up in bed); (c) ventricular tachycardia; (d) partial or complete heart-block; and (e) true nodal rhythm—a very long pause between the second and first sound of the heart that gives one the impression that the heart may not beat again is sometimes an evidence of digitalis toxemia. Fortunately these signs can, in almost every instance be determined clinically without the use of instrumental means. As to the second group, i.e., its effects on other organs, the symptoms of such effects are most insistent and are Nature's own efforts for safety. They are nausea, vomiting and diarrhea. When such symptoms follow the first few doses of the drug, they are almost always the result of a local irritation of the stomach itself and should not constitute a contraindication to the use of the drug but rather to the way of administering it. However, when they occur after some days of its use or after the administration of large doses, they call for its prompt discontinuance. The suggestion that extreme hunger and hunger pangs are among the earliest evidences of digitalis toxemia has been made by Neuhof, and the author has often confirmed this finding. These symptoms may precede the major symptoms by a day or two. If an intercurrent disease is present, which is associated with fever, the dosage of digitalis should be greatly increased because of the clinical observation that its effects are decidedly lessened in the presence of temperature. Of course, no one should give the drug for the treatment of acute endocarditis as such, nor in the hope that it will control a rapid action of the heart from any cause, except where there is an old lesion present, preceding the acute exacerbation. It is usually only when such a lesion is rheumatic in origin that such control will be evident. The use of the drug for the purpose of slowing the heart is in acute disease perhaps the commonest therapeutic error in medicine.

TIME OF ADMINISTRATION.—No matter what preparation is employed, it is best to give it after meals, rather than on an empty stomach. It is seldom necessary to administer it more than four times a day. When once the physiological effect is produced, it continues, and two doses each day are sufficient.

Opium.—Next to rest and digitalis, opium is the most necessary agent in the treatment of heart-failure associated with chronic valvular disease. It is absolutely necessary to relieve the severe pain that frequently accompanies this disease, and should then be given in the form of a hypodermic of **morphin**. For the distressing dyspnea it has no equal in our armamentarium. For sleeplessness it is the only agent which can always be relied upon. It produces a more constant lowering of blood-pressure than any other medicine. It does not cause as great a fall as the nitrites do, but produces a more lasting effect. This it does through its calmative effect upon the nervous system. The nervous element in most cardiac patients is responsible for an increase of from 10 to 30 mm. Hg, and this is overcome by small doses of the narcotic. There are very few contraindications to its temporary use in cardiac disease. Of course, digestive disturbances following its use are not uncommon,

but they are not any more marked than they are in patients suffering from other diseases; indeed, one often feels that they are less so. The drug is contraindicated in acute gastric dilatation as pointed out elsewhere. It is not absolutely contraindicated in renal disease if the kidneys are moderately active. While it is not excreted through the kidney, yet in case of any patient suffering from a very marked diminution in urine, unless other indications are absolute, it should be employed with caution. It is difficult to say whether such patients go into coma because of the kidney disease or because of the effect of the narcotic, but it is better practice to withhold it unless the distress is very great.

ADMINISTRATION.—When the symptoms are not decidedly urgent, the use of the deodorized tincture in doses of $7\frac{1}{2}$ minims (0.5 c. c.) every four hours is commonly sufficient. This may well constitute the first prescription in any case whenever the patient has not slept for several days or is suffering distress. Sometimes **codein** may be substituted for the opium with fewer disagreeable effects upon the digestive tract. Codein is especially valuable in the coughs of the cardiac patient. In the presence of severe symptoms morphin from grain $\frac{1}{3}$ (gram 0.0216) to grain $\frac{1}{2}$ (gram 0.0324) hypodermically is commonly necessary. When the drug itself is given by mouth it is best to combine it with a pleasant menstruum, as the taste and odor are disagreeable to some patients. Either the elixir adjuvans or the aromatic fluid extract of cascara sagrada are useful for the purpose. Of course its use should not be continued any longer than is necessary to relieve the urgent symptoms, but on the other hand it should never be withheld because of the fear that the patient may contract the habit, or because of any mawkish sentimentality as to “doping.” It is almost an unheard-of thing in a large hospital service to meet with a patient who has contracted the habit from the employment of the drug for the relief of the symptoms of true cardiac disease. The cardiac patient who requires the constant use of a narcotic for a long time is likely to die in any event, and it is cruelty not to afford relief when it can be obtained. At the present time, there is, on the part of the younger practitioners, a disinclination to use the “dope” as it is called, or any other agent which only relieves the symptoms of disease rather than the cause of the disease itself. The attainment of any such object as a cure in the treatment of cardiac disease is only an evanescent dream. In the present state of our knowledge the treatment of symptoms must constitute at least 90 per cent. of our therapy, and opium is easily the king of all agents which may be used in relieving the symptoms of cardiac disease. It is always difficult to impress sufficiently upon the mind of the student that opium does not kill through the action on the heart, but rather through action on the respiration, and that it is not a heart depressant.

Other Drugs of Use in Cardiac Diseases.—**CAFFEIN.**—Caffein itself is of a limited use as a diuretic, except as a temporary stimulant; it is of little value as far as the heart itself is concerned. In the form of diuretin, grains $7\frac{1}{2}$ to grains 15 (gram 0.492 to gram 0.972), four times

a day, or **theocin**, grains 2 to grains 5 (gram 0.13 to 0.324), it is an efficient diuretic, particularly of service where there is coincident disease of the kidney. If **digitalis** of unquestioned efficiency is employed in sufficiently large doses for a week, with no effect on dropsy, then **diuretin** should be substituted for three or four days. Frequently such an alternation is useful throughout the whole course of treatment.

NITRITES.—**Nitroglycerin** is of value as a means of relieving acute symptoms, rather than for the production of any permanent effect.

Frequently the administration of the drug at regular intervals will prevent the occurrence of painful attacks. In other instances it is best given just before the patient goes out for a walk or immediately after meals before any exertion.

It is for the relief of paroxysms of anginal pain and dyspnea consequent on cardiac disease that its most striking effects are observed. The effect of a tablet of **nitroglycerin** (grain 1/100 [0.00065 gram]), when allowed to dissolve under the tongue (and this is the best way of administering it), is apparent in less than three minutes, and continues for half an hour, but the symptoms for which it was given often do not return for days thereafter. The action of **nitrite of amyl** is generally unsatisfactory.

STRYCHNIN.—The effect of **strychnin** is really exerted upon the spinal nervous system, and it does not have any appreciable effect upon the unstriated muscle of the heart. It does stimulate the general muscular system, and increases the depth of respiration. It does not (as has been so generally stated in the text-books of the last decade) act as a tonic on the heart. Its effects have no possible resemblance to the action of **digitalis**. If the symptoms of **neurasthenia** are present it commonly makes the patient feel worse.

ATROPIN.—The author has not found **belladonna**, or **atropin**, to be of any decided service in relieving minor symptoms. To alleviate the nocturnal attacks of dyspnea which prevent the patient from sleeping, the use of a full dose, grain 1/100 to grain 1/75 (gram 0.00065 to gram 0.00086), given late in the evening by hypodermic, will sometimes ensure regular breathing throughout the night. The author has never been able to convince himself of the efficacy of the **belladonna** plaster in relieving cardiac pain.

BROMIDS.—For the relief of many of the minor symptoms **bromid** does what **opium** will do for the alleviation of the major symptoms. It frequently satisfactorily relieves palpitation, quiets nervous apprehension, and thus soothes the tumultuous action of the heart. It is of especial service in the aortic cases. By quieting the nervous system it materially lowers blood-pressure. With the exception of **opium** its effect in this respect is more lasting than when the pressure is lowered by any other agent. It is well to continue its use on and off, alternating with **potassium iodid** and with **Crataegus**. It must be given in full doses, 20 or 30 grains (1.30 or 1.95 grams) two or three times daily. Less than 20 grains (1.30 grams) at a dose is absolutely useless. One cannot too

VOL. VI.—13.

often repeat that the dosage of all drugs in cardiac disease must be high as compared with their use in other conditions. Mistaken dosage accounts for far more failures in cardiac therapy than mistaken indications. When there is bromid intolerance or severe acne from its use, *valerian* does to some extent take its place, pharmacologists to the contrary notwithstanding.

CALOMEL AND MERCURY.—The indication for the use of the mercurials is clear enough in luetic cases, but their occasional service in other cases is not so clear; yet the clinical evidence of their value is unquestioned. Frequently in an undoubted rheumatic mitral lesion, with steady progression, and in which nothing seems to stop the dropsy and dyspnea, the use of calomel, either as a single dose, or given three times a day, will produce a marvelous result. It is believed that much of this is due to the diuretic effect of the mercury. Therefore, it is a good rule in any case that has not reacted to ordinary medication to prescribe a *Niemeyer pill* containing calomel, squills, and digitalis, *aa* grain 1 (0.065 gram) t. i. d. for three days.

The drug must not be given for more than three days at a time because of the danger of salivation. Sometimes *blue mass* may be substituted for the calomel.

ACONITE.—The field of usefulness of aconite in valvular disease is a very limited one. Occasionally in aortic disease with a very much perturbed heart, cyanosis, cardiac pain and oppression, the use of a few doses of the tincture of aconite affords relief when nitrites fail. The physiologic effect of the drug is only produced in such cases by the use of enormous doses. It appalls most practitioners to be told that the dosage should be between 20 and 30 minims (1.25 and 1.895 grains) repeated every three hours. The writer has not found its continued use successful in controlling symptoms. Such large doses do not produce the toxic effects which commonly result in normal individuals from the injection of a similar dosage.

OXYGEN.—Oxygen is occasionally of service in the cyanosis of decompensation. One can never tell definitely in which cases it will be beneficial. At times oxygen does give decided relief. It is given for from ten to twenty minutes every two hours.

SPARTEIN.—Sparteïn is occasionally of service, and may be given during an interval when the digestive tract is rebellious to the digitalis bodies. It sometimes produces prompt diuresis. The dosage is grain $\frac{1}{2}$ (0.0324 gram) every four hours.

ADONIS VERNALIS.—This drug has not been successful in the author's experience.

APOCYNUM.—This is the vegetable trocar of the eclectics, and has a well-deserved reputation in patients who, figuratively speaking, are unaware of the fact that they have a stomach. The local action on the stomach is often irritating, and the drug must frequently be discontinued. The physiological action is due to the digitalis-like bodies. Where it does act well, the results are truly marvellous. The dropsy disappears

as if by magic. The dosage is 10 minims (0.6 gram) every four hours. An active principle has been on the market, but has not been satisfactory.

SQUILLS.—Squills contains the digitalis-like bodies, and would be ideal were it not for the local irritating effect on the stomach. In the mercury pill its synergist action is of great service. The dosage is from 1 to 5 grains (gram 0.065 to gram 0.324) of the powdered drug.

Therapeutic Measures Other Than Drugs.—**NAUHEIM BATH.**—Before the war the Nauheim baths had acquired, especially among the laity, a widespread vogue. Because of the special physical effect perceived by the patients themselves, as well as because of blood-pressure changes recorded by enthusiastic Spa physicians, the hope was planted in the patient's minds that not only could relief of symptoms be had, but that actual cure was to be attained by the baths. There is no question but that well-defined physiologic effects occur following these baths. The skin is reddened and blood-pressure raised or lowered, depending upon the temperature of the bath.

The Nauheim bath consists in immersion in a saline bath, containing a large amount of carbon dioxid. The physiologic effects depend (1) upon the temperature of the water, and (2) upon the contents of the water. The effect of a cold bath is well-known—a lowering of the pulse-rate and increase of blood-pressure—whereas a hot bath causes an increase in pulse frequency. In the Nauheim bath, in addition to the temperature, the effect depends upon the carbon dioxid liberated. There is no direct effect on the heart itself from the use of the bath; its gain is an indirect one. The dilatation of the superficial capillary circulation as well as the deep vessels increases their capacity and thus takes the burden off of the heart for the time being. The dilatation of the vessels of the skin is simply due to the carbon dioxid contained in the bath; the salts also have a similar effect but to a less degree. This produces a sensation of tingling and warmth over the whole body, thus making the bath seem much warmer than it really is. Within five minutes, there is a perceptible diminution in the respiration and the pulse is definitely slower within ten minutes. The composition of the bath consists of carbon dioxid, calcium chlorid and sodium chlorid. In the baths at Nauheim, the carbon dioxid is contained in the spring water. The ordinary method employed at Nauheim is as follows: A hot bath lasting from five to ten minutes is given at a temperature of 95° F. (35° C.); after this the temperature is reduced one degree Fahrenheit each day until 86° F. (30° C.) is reached. At the same time, the bath is prolonged one minute longer each day and the amount of salt is gradually increased. After the bath, the patient should be placed in a recumbent position and lightly covered; he must remain quiet for an hour or two, care being exercised that perspiration does not occur. A full course consists of twenty baths, followed by a period of rest of a month or so, to be followed by a second course. The same physiological effects may be obtained from the artificial Nauheim baths administered in the home.

Many of the large commercial drug houses put the salts and acid in convenient form for the ready making of the Nauheim baths.

THE NAUHEIM BATH AT HOME.—In the home it is advisable to begin with the so-called salt bath. The carbonated effervescing baths should never be employed at the first treatment. The first bath contains 5 pounds of salt and 6 ounces of calcium chlorid in 45 gallons of water. The quantity of salt and calcium is added, 1 pound of the former and 1 ounce of the latter until 10 pounds of salt and 11 ounces of calcium chlorid are employed. At the tenth bath, the carbon dioxid is introduced. The first effervescent bath consists of: 50 gallons of water at a temperature of 90° F. (32.22° C.) and 5 pounds of sodium chlorid, 1 pound of calcium chlorid, 8 ounces of sodium bicarbonate and 225 c.c. HCl. The first three ingredients are mixed in the water and then the acid is slowly added and stirred; the amount of sodium bicarbonate and acid are gradually increased day by day thus producing an increased elimination of carbon dioxid. At first, the duration of immersion is from three to four minutes. This is increased from one to two minutes at each succeeding bath. The first bath is given at a temperature of 96° F. 35.6° C.). This temperature is lowered by 1° F. (0.55° C.) every second bath, down to 93° F. (33.9° C.). After the bath, the patient goes to bed for at least an hour; a hot water bottle is put in the bed; chilliness means that there should be an increase in temperature of the bath. The baths may conveniently be given for two days in succession and, if circumstances permit, on the third day exercises may be employed. From twenty to thirty baths constitute a course. As a complementary measure, exercises are usually given in connection with the baths at Nauheim. These exercises were originally advocated by Schott and may be varied. Any of the ordinary anticonstipation exercises, not done too actively, will answer, the chief point being that the patient should not be tired as a result of the work.

EXERCISE.—When compensation has not been seriously disturbed the exercise of the patient's daily avocation is sufficient. When, however, there has been an attack of decompensation, even during convalescence, recovery is often materially hastened and the patient's own condition improved by careful exercise. At first, these exercises should be administered by the physician himself, or by a competent assistant. In the beginning they should consist of ordinary resistance motions. Unless the exercise prescribed is pleasurable to the patient, it will seldom be continued and unless some one else goes through it with him at the time, he will soon tire of it. In the offices of those devoting themselves to cardiac disorders, it is customary to have the nurse accompany the patient through such exercises at regular intervals. The following are the exercises as recommended by Schott himself in the Brunton lectures:

1. The arms are to be raised slowly outward from the side until they are on a level with the shoulders. After a pause they should be slowly lowered.

2. The body should be inclined sideways as much as possible toward the right and then toward the left.

3. One leg should be extended as far as possible sideways from the body, the patient steadying himself by holding on to a chair. The leg is then dropped back. The same movements are repeated by the other leg.

4. The arms are raised in front of the body to a level with the shoulders and then put down.

5. The hands are rested on the hips, and the body is bent forward as far as possible, and then raised to the upright position.

6. One leg is raised with the knee straight forward as far as possible, then brought back. This movement is repeated with the other leg.

7. With the hands on the hips, the body is twisted round as far as possible to the right, and then again to the left.

8. With the hands resting on a chair and the back stiff and straight, each leg is raised as far as possible backward, first one, then the other.

9. With the fists supinated, the arms are extended outward, then inward at the level of the shoulders.

10. Each knee is first raised as far as possible to the body, then the legs extended.

11. This movement is the same as 9, but with the fists pronated.

12. Each leg is bent backward from the knee and then straightened.

13. Each forearm is bent and straightened from the elbow.

14. The arms are brought from the sides forward and upward, then downward and back as far as they will go, the elbows and the hands being straight.

15. The arms are put at a level with the shoulders and then bent from the elbows inward and again extended.

16. With the arms in front at a level of the shoulders and the hands stretched, the arms are opened out sideways and then brought together.

17. The arms are bent from the elbows, lifted outward and extended. The essential part of the movement is that the movement be slow and regular.

Practically few patients who are able to be about can afford the time or money for such luxury. Instead of this, walking on the level is a form of exercise within the reach of all and is quite as efficient. Common sense will teach how many blocks the patient can walk without fatigue and the number can gradually be increased. The value of Nauheim baths as a therapeutic measure is a somewhat debatable one. This much may be said,—they are of value only in the treatment of the patient who is suffering from the minor symptoms of decompensation, provided that he feels better after their use. Certainly they are not indicated in the presence of any of the major symptoms of decompensation. The effect of the Spa surroundings is often of more value than the baths themselves. They serve to bring the patient under medical supervision from time to time, which is of greater possible value to the

patient than the reaction to the bath. Human nature demands that something physical be done, aside from the mere rehearsal of symptoms and advice and these baths are of service, just as electricity, high frequency, or any other similar physical measure would be. However, psychophysics methods to be followed in a religious manner such as the Schott and Oertel methods have never become popular in this country.

The aim of these various systems is to increase the compensatory reserve of the heart muscles of the body, in a pleasant and agreeable way, with little discomfort to the patient. It is only applicable to a limited number of obese and wealthy patients, and is best carried out in an institution devoted to this work.

THORACENTESIS.—Patients suffering from severe decompensation should be examined daily for indications of fluid in the serous cavities. It is particularly apt to occur insidiously in the pleural cavity. The right side is more often affected than the left. This may be ascribed (1) to the fact that most cardiac patients lie on the right side, and (2) to the obstruction of the mouth of the major azygos veins from the pressure of the dilated right heart.

Thoracentesis should be done whenever breathing is markedly interfered with, in the presence of a demonstrable effusion. Left-sided effusions must be especially watched, and whenever the effusion extends above the lower angle of the scapula, it should be drawn off. On whichever side it may be, when it is up to the fourth rib, the chest should be aspirated. If there is any fear of collapse a small amount of **novocain** may be injected at the site of puncture, five minutes previous to the aspiration. Sometimes the operation is best done with the patient in the recumbent position.

PARACENTESIS ABDOMINIS.—Paracentesis should not be lightly undertaken until all other methods of relief of the ascites have been tried because it often disappears. Sometimes ascites develops before there is a marked general edema. In such cases there is often a preëxisting cirrhosis of the liver. This would not of itself produce stasis in the abdominal cavity, but the added congestion due to the weakness of the heart is sufficient to obstruct the portal vessels and produce the ascites. The ascites should be aspirated whenever it is sufficient to interfere with respiration. Unfortunately it frequently soon returns.

In the presence of well-marked edema of the legs which does not react within four days to digitalis, the insertion of two aspirating needles in each limb, and occasionally a small one in the scrotum, is followed by a profuse loss of fluid, often amounting to a couple of quarts. Southey's tubes are seldom in the possession of the practitioner, and the aspirating, or large caliber hypodermic needles, are just as efficient. Ordinary care is necessary to prevent infection. The skin should be treated just as carefully as prior to an ordinary operation. After the puncture the needle and leg should be surrounded with sterile gauze. The excreted fluid is irritating, and if the discharge continues for more than a few days it produces eczema, causing the practitioner to fear.

that the wound is infected. This is rarely the case, and if a weak carbolized or boric-acid compress is applied to the limb, it is still less likely to occur.

Whenever digitalis fails, before condemning the drug, one should drain all of these locations, chest, abdomen, skin and bowels, as frequently no physiological effect is apparent until the edema has been partially relieved by such physical measure.

VENESECTION.—This is indicated in any case of sudden marked cyanosis and evident right heart-failure. In a case with high blood-pressure, presenting any symptoms, not reacting to or relieved by ordinary measures, from one pint to one quart of blood should be withdrawn. The most satisfactory technic is as follows: After the site at the bend of the elbow has been cleansed, a bandage is tied about the arm, which is allowed to hang down in order to distend the veins, and an incision is made along the side of the most prominent vessel at the bend of the elbow. The knife is inserted under the vein and it is cut outward. Bleeding by means of an intravenous needle to which a rubber tube is attached eliminates the sight of blood and extravasation, but the author has not found this method satisfactory, unless a large needle such as is used in the transfusion of blood is employed and such a needle is seldom handy. In case it is used, it should be directed from above downward. Cocain is seldom necessary. If the cuff of an ordinary blood-pressure instrument is applied about the arm, and air pumped in to a point midway between the systolic and diastolic pressure and kept there, the flow of blood is more satisfactory than when an ordinary tourniquet is employed.

REST IN BED.—The patient must remain in bed until all of the demonstrable effusions in the serous cavities have disappeared, and the edema has left the extremities and the dyspnea is not produced on slight movement in bed. A good plan is to wait a week after the edema has disappeared from the legs, before allowing the patient to leave the bed. In the meantime, during treatment, the patient should be instructed to make up and down movements of the extremities for a period of five minutes, three or four times daily. When he does get up, he should be warned of the likelihood of vertigo, which is common in any one who has remained in bed for several days. After recovery to the point to be able to get about without dyspnea or edema, the patient is by no means able to go back to work, if it entails much physical labor. Two or three weeks should be spent in convalescence. As soon as the immediately serious symptoms are on the wane the information should gradually be imparted to the patient that he will certainly have a recurrence of his illness. This must be repeated, again and again, because these patients are naturally optimistic and, when they find themselves apparently free from symptoms, live in a fools' paradise and nearly always think that the ailment has departed, much like any acute infectious disease. It requires some courage on the part of the practitioner to tell the patient, frankly, the exact nature of the remaining lesion,

as it takes some of the edge from the thanks and gratitude showered upon him, but it is as necessary as prescribing a medicine. One must be almost brutally frank, especially on the last visit. If the labors of the former occupation were responsible for the ill health, then the patient should be advised to seek a new one, even though it involves a financial loss, because, after all, a year or two of extra life cannot be measured by any financial standard.

If, on the other hand, as is most commonly the case, the break in compensation was due to infection, a change of occupation is not indicated, unless the attack has left the patient unable to perform his former work without the production of symptoms. Finally, it should be impressed upon him as a bounden duty, to return to the physician for a physical examination, at least every two months. It may be argued that there is little change to be detected in the heart itself by such examination, and this is quite true. It is mostly by interrogation as to the presence or absence of symptoms that one can arrive at an estimation of the condition of the heart; but the layman feels that the information gleaned by physical examination is paramount. He thinks that he can judge symptoms for himself. Upon the progression or regression of symptoms between such examinations will depend the necessity of change of occupation and of treatment.

Outline of Treatment for Patient Suffering From One or More of the Marked Symptoms of Decompensation.

First day:

Absolute rest in bed.

Woolen under-clothing.

Blankets.

Hot water bottle to feet.

Nurse ordered to be in constant attendance for one week or more.

No visitors.

Warning to friends as to the seriousness of the condition.

Suggestion that religious and financial matters be broached to the patient by a relative, not by physician.

Reassurance of the patient as to his safety.

Starvation diet for twelve hours.

Dry diet thereafter.

Local applications to chest if needed.

Urine to be measured for twenty-four hours, also fluid intake.

Sample of urine to be sent to laboratory for examination.

If symptoms are severe, hypodermic of morphin, grains $\frac{1}{4}$ to grains $\frac{1}{2}$ (gram 0.0162 to gram 0.0324) at once; also calomel, grains 2 (gram 0.130), with compound jalap powder, $\frac{1}{2}$ dram (1.95 gram), at bed-time.

Leave following prescription:

- R** Tincturæ opii deodorisati.....3ii (7.50 c.c.)
 Tincture digitalis.....3iv (15 c.c.)
 Elixir adjuvans.....q. s. ad 3ii (60 c.c.)
 Sig.: 3i (3.75 c. c.) every four hours.

See patient in twelve hours if the symptoms are severe, otherwise next day and each succeeding day until there is some improvement.

In hospital practice, where the decompensation is acute and the patient has not had digitalis, the Eggleston method is a preferable way of administering the digitalis.

Second day:

Dry diet.

No liquids with meals.

Meat, bread, potato, cereal (salt-free).

Liquids restricted to two pints in twenty-four hours, preferably milk, black coffee or tea.

Continue opium and digitalis.

Aloin or cascara pill at bed-time.

Symptomatic treatment of other complaints.

Third day:

Discontinue opium. If sedative is necessary, use a milder one.

Continue digitalis and other measures as above.

Fourth day:

If there is no decided relief in the presenting symptoms in seventy-two hours, give a Niemeyer pill t.i.d., alternating with diuretin and Karell diet.

Fifth day:

If no results are obtained, paracentesis of cavities and tissues must be seriously considered. If after two weeks, there has been no decided improvement, it is well to fortify one's self by calling in counsel. It is only natural that friends of the patient wish a change by this time, and unless something is done, the practitioner is likely to be supplanted; furthermore, the magical change that sometimes takes place in the patient's condition within a day after a consultation, even though there has been no change in medication, is sufficient excuse for the procedure. It can only be explained by the basis of renewed hope and additional determination to recover.

REFERENCES

- ANDERS. Practice of medicine. 13th Ed., 1917. W. B. Saunders & Co., Phila.
 ABRAHAM, R. Elements of prognosis in chronic valvular disease of the heart.
 N. Y. State Jour., April, 1910, iv, No. 4, p. 175.
 BOOSE, N., AND MARKS. The use of digipuratum in heart disease. Arch. Int.
 Med., April, 1911, vii, 551.
 BROADBENT, W. H. Heart disease. 4th Ed. Balliere, Tyndall & Cox, London.
 BROOKS, H. Syphilis of the heart. Inter. Clinics., 1915, i, Series 25, p. 134.

202 CHRONIC VALVULAR DISEASE OF THE HEART

- BROWN, P. K. Artificial Nauheim baths in chronic heart disease. *Boston Med. and Surg. Jour.*, 1906, clv, 276.
- BRUCE. The principles of treatment and their applications in practical medicine. 1912, Lea Bros. & Co., Phila.
- BRUNTON, T. LAUDER. Lectures on the action of drugs. 1897, 1st Ed., p. 368. MacMillan & Co., London.
- CABOT. The association of diastolic murmurs with mitral stenosis. *Trans. Assoc. Amer. Phys.*, 1914, xxix, p. 22.
- COOMBS, CAREY. Index of prognosis. 1st Ed., 1915, p. 356. Wm. Wood & Co., New York.
- CUSHNEY, A. R. Pharmacology and therapeutics. 5th Ed., 1910. Lea & Febiger, Phila.
- DIEULAFOY. Practice of medicine. 2nd Ed., 1912. D. Appleton & Co., New York.
- EGGLESTON, C. Digitalis dosage. *Arch. Int. Med.*, 1915, i, 1.
 ——— Some newer concepts in digitalis therapy. *Am. Jour. Med. Sc.*, cix, No. 5, p. 625; also *Jour. Am. Med. Assoc.*, March 13, 1920, lxxiv, 733.
- ELSNER. Monographic medicine. 1916, 1st Ed. D. Appleton & Co., New York.
- EPSTEIN, J. *Arch. Diag.*, Jan., 1917, x, 59.
- FONTANE, S. W. Statistics of frequency of syphilis of the aorta. *So. Med. Jour.*, June, 1918, xi, 278.
- GERHARDT. Die Klappenfehler. Wien. 1913.
- GIBSON, G. H. Diseases of the heart and aorta. 1885, 3rd Ed. MacMillan & Co., New York.
- GOODMAN. Mitral stenosis. *Am. Jour. Med. Sc.*, 1919, Nos. 1, 2, and 3.
- HALE, W. The comparative strength of digipuratum and a comparative study of digalen. *Jour. Am. Med. Assoc.*, Jan. 1 and Jan. 8, 1910, liv, No. 2, pp. 129 and 351.
- HATCHER, R. A., AND BRODY, J. G. The biological standardization of drugs. *Am. Jour. Pharm.*, 1910, lxxxi, p. 360.
- HIRSCHFELDER, A. D. Diseases of the heart and aorta. 1919, 3rd Ed. Lippincott & Co., Phila.
- LIBMAN, E. Classification of the cardiac murmurs. *Med. Clin. North Am.*, Nov., 1917, i, No. 3, p. 573.
- LONGCORE, W. The relation of the origin of aortic insufficiency to syphilis. *Arch. Int. Med.*, Jan., 1915, xi, 14.
- MATTHEW. Vasodilatation in high blood-pressure. *Quart. Jour. Med.*, April, 1909, ii, 261.
- McKENZIE. Diseases of the heart. 1917, 3rd Ed. Oxford.
 ——— Symptoms and their interpretation. 1918, 2nd Ed. Oxford.
- McCALLUM AND McCLURE. Artificial lesions of the mitral valve. *Johns Hopkins Hosp. Bull.*, 1906, xlv, 260.
- MOON. The prognosis and treatment of diseases of the heart. 1st Ed., 1912. Longmans, Green & Co., New York.
- NEUHOF AND SELIAN. Clinical cardiology. 1917, 1st Ed. MacMillan & Co., New York.
- NORRIS, G. U. Studies in cardiac pathology. 1917. W. B. Saunders & Co., Phila.
- NORRIS, G. U., AND LANDIS, H. R. W. Diseases of the chest and the principles of physical diagnosis. 1917, 3rd Ed. W. B. Saunders & Co., Phila.
- NORRIS AND PETERHOF. The topography of the cardiac valves as revealed by the x-ray. *Am. Jour. Med. Sc.*, 1915, cxlv, 225.
- PARDEE, H. *Am. Jour. Med. Sc.*, Nov., 1920, lxxv, 1258.
- PITT, N. Tricuspid disease in Albutt's system of medicine. 2nd Ed., 1919.
- SANSOM. The signs of diseases of the heart and thoracic aorta. 1892, 3rd Ed. A. E. Griffin & Co., London.
- SEARS. *St. Paul Med. Jour.*, Mar., 1917, iv, 272.

- SLEMMON AND GOLDSBOROUGH. The influence of pregnancy and labor on the heart. Johns Hopkins Hosp. Bull., 1908, xix, No. 208, p. 194.
- STEWART. Hypertrophy of the heart. Arch. Int. Med., 1908, i, No. 1, p. 102.
- TALLEY. Some criteria underlying prognosis in certain forms of cardiac insufficiency. Penn. Med. Jour., Feb. 16, 1919, xix, 338.
- THORNE, L. The Nauheim treatment. 5th Ed., 1918. Balliere, Tyndall & Cox, London.
- TICE, F. The clinical determination and significance of some of the peripheral signs of aortic insufficiency. Ill. Med. Jour., Sept., 1911, xx, 271.
- WARTHIN. The persistence of active lesions and spirochetes in the tissues of clinically cured and inactive syphilis. Trans. Assoc. Am. Phys., 1914, xxix, 417.
- WIGGERS, C. J. The circulation in health and disease. 1915. Lea & Febiger, Phila.
- WILLIAMSON, C. F. Forchheimer's Therapeutics of heart disease. 1914. D. Appleton & Co., New York.

CHAPTER IV

DISEASES OF THE PERICARDIUM

FREDERICK TICE, M.D., F.A.C.P.

- Pericarditis, p. 205—Definition, p. 205—Etiology, p. 206—Bacteriology, p. 208—Clinical varieties, p. 209—Acute plastic pericarditis, p. 209—Symptomatology, p. 209—Clinical history, p. 209—Pain, p. 209—Fever, p. 209—Palpitation and dyspnea, p. 209—Physical findings, p. 209—Auscultation, p. 209—Palpation, p. 210—Diagnosis, p. 210—Pericarditis with effusion, p. 211—Etiology, p. 211—Symptomatology, p. 211—Clinical history, p. 211—Physical findings, p. 211—Roentgenologic examination, p. 213—Diagnosis, p. 216—Clinical varieties of acute pericarditis, p. 217—Pericarditis sicca, p. 217—Serofibrinous pericarditis, p. 217—Purulent pericarditis, p. 217—Hemorrhagic pericarditis, p. 217—Tuberculous pericarditis, p. 217—Syphilitic pericarditis, p. 218—Chronic pericarditis, p. 218—Treatment, p. 218—Paracentesis pericardii, p. 220—Course, duration and termination, p. 222—Prognosis, p. 222—Morbid anatomy, p. 223—Pathologic physiology, p. 224.
- Adherent pericardium, p. 225—Synonyms, p. 225—Definition, p. 225—Etiology, p. 225—Symptomatology, p. 225—Physical signs, p. 226—Roentgenologic examination, p. 228—Diagnosis, p. 229—Treatment, p. 230—Medical, p. 230—Surgical, p. 230—Prognosis, p. 231—Morbid anatomy, p. 232—Pericardial lesions, p. 232—Mediastinal and neighboring tissue lesions, p. 232—Cardiac lesions, p. 233—Hepatic lesions, p. 233—Pathologic physiology, p. 233.
- Hydropericardium, p. 235—Definition, p. 235—Etiology, p. 235—Symptomatology, p. 236—Physical signs, p. 236—Diagnosis, p. 236—Treatment, p. 236—Prognosis, p. 237.
- Hemopericardium, p. 237—Definition, p. 237—Etiology, p. 237—Symptoms and signs, p. 237—Diagnosis, p. 238—Treatment, p. 238—Prognosis, p. 238—Morbid anatomy, p. 238.
- Pneumopericardium, p. 238—Definition, p. 238—Etiology, p. 239—Symptoms and physical signs, p. 239—Roentgenologic examination, p. 240—Diagnosis, p. 240—Treatment, p. 241—Prognosis, p. 241—Morbid anatomy, p. 241.
- Neoplasms of the pericardium, p. 241—Malignant neoplasms, p. 241—Symptoms and physical signs, p. 243—Diagnosis, p. 243—Treatment, p. 243—Prognosis, p. 243—Benign neoplasms, p. 243.
- History, p. 243.

PERICARDITIS

Definition.—Pericarditis is an inflammatory involvement of the pericardium, either as a primary clinical entity or secondary to some other disease.

In some instances the inflammatory process may be limited to the pericardial sac, as determined by the predominating clinical symptoms and signs, or by the anatomic findings; more frequently there is an associated myocarditis, an endomyocarditis, or the external surrounding

structures of the pericardium are also involved. In discussing the etiology of pericarditis, Sibson makes the following statement: "Inflammation of the surface of the heart and the lining of the pericardial sac occurs so very rarely by itself that we cannot practically regard it as a distinct disease."

Von Jurgensen, in his article on endocarditis, without reference to the etiology, but considering chiefly the local anatomic changes, uses the expression "pancarditis"—and this will be the diagnosis of the future. But he who makes this diagnosis must know how to distinguish the various parts which compose the whole, and to weigh the relative importance of each. The object should be, of course, in each individual case to analyze the composite picture of pancarditis with its constituents—endocarditis, myocarditis and pericarditis.

Etiology.—For many reasons a bacteriologic classification is the ideal one, but this is not possible at the present time. The subdivision of acute, subacute and chronic is not satisfactory or acceptable for an etiologic basis, as it applies to the clinical course and renders no assistance as to the actual cause. The old classical and generally accepted classification of primary idiopathic and secondary pericarditis is open to suspicion and doubt, more so with the increased and growing knowledge of the bacteriology of pericarditis, the modes of infection and the associated pathology. While it must be admitted that a primary idiopathic pericarditis is possible and may occur, the frequency of such is gradually decreasing; even the causative factors previously accepted are losing their significance except as contributing factors. Exposure to cold, and trauma have been accepted as potent factors in the production of idiopathic pericarditis, but bacteriology has deprived them of much of their previously accepted influence. No doubt, in some instances, they have an indirect or contributing influence in reducing the general or local resistance, as occurs in many other diseases, but they can hardly be accepted as the primary essential cause. Too often careful examination reveals some obscure focal infection, such as small imbedded but infected tonsils, a pyorrhea with infected teeth, an infected gallbladder, tracheobronchial adenitis or pulmonary infection, perhaps without clinical symptoms—conditions whose significance until recently was underestimated. Even where it is impossible to detect clinically some focus of infection, the anatomic examination demonstrates the presence of tubercles or organisms.

Secondary pericarditis may occur in practically any infectious disease, the infecting organism reaching the pericardium by means of a systemic infection, or the pericardium may become involved by direct extension by contiguity.

Of the primary diseases with which pericarditis is most frequently associated, rheumatism stands preëminent; it is quite analogous to endocarditis. Statistics are variable, but age plays an important rôle. In the young, not only the endocardium, but the myocardium, is prone to infection; in the adult, the joints alone may be involved. Pericarditis usually occurs as a complication of the rheumatic infection, during or

subsequent to the arthritic manifestations, but, not infrequently, the pericardial involvement occurs as the initial disease and the arthritis develops later. A proper appreciation of the importance and etiologic relation of rheumatism and pericarditis may be held in a review of the literature. In 326 cases of rheumatism, Sibson found a pericarditis in 63; Latham reports 7 in 136; while other authors state that it occurs in from 30 to 50 per cent of rheumatism. Of the 94 cases of pericarditis observed in the County Hospital, 30 occurred as a complication of articular rheumatism. The severity of the infection as well as the duration of the attack is of some importance. Due to the lowered general and local immunity, the pericarditis frequently appears at the height of the infection but is not uncommon in the recurring, subacute exacerbations of the arthritis. Males are relatively more prone to rheumatic pericarditis, due no doubt to the influence of occupation and greater exposure to contributing causes. Tonsillitis must be considered a close rival of rheumatism; perhaps the former even outranks the latter if the primary or focal infection in rheumatism be considered as a separate disease. The tonsil, with or without clinical symptoms, due to the investigations in local infection, is rapidly becoming more and more incriminated. Chorea, particularly in children, accompanying or following a tonsillitis or arthritis, is a fairly frequent cause. This might be suspected in the light of the investigations of Poynton and Paine, as well as subsequent workers, that all these diseases have been associated with the same organism.

A general sepsis, either primary or secondary, or a pyemia from any form of infection is a fruitful cause. To this group belongs the systemic infection accompanying pneumonia and typhoid fever, the former a frequent cause of pericarditis, the latter rarely producing pericardial involvement. Syphilitic infection must be mentioned among the possibilities, but how frequently this is a cause has not been determined. Of the eruptive fevers, scarlet fever deserves special mention; less important are measles and smallpox. Diphtheria may act as a cause, but the associated mixed infection is usually the exciting factor.

Tuberculosis of the pericardium as a primary disease is extremely rare, but it has been reported by Scaglios in a personal observation; he also refers to 7 similar cases. The secondary type of the disease is relatively frequent.

Gonorrheal infection is by no means a rare cause of pericarditis. Most frequently the pericardium becomes involved, accompanying or following a previous complication, such as a gonorrheal arthritis, endocarditis or prostatitis.

Chronic wasting diseases, such as nephritis, diabetes, carcinoma and aortic aneurysm, constitute a well-recognized group, frequently complicated by a pericarditis and often terminal. Pericarditis complicating a terminal nephritis is comparatively frequent and is usually designated as a renal pericarditis. In some instances it is probably due to a terminal infection but more frequently is associated with the changes accompanying a renal insufficiency and a protein retention.

In the group of diseases producing pericarditis by extension by contiguity, pneumonia and pleurisy are the most frequent and, in the order of importance, rank next to the rheumatic infections. Pericarditis is a more frequent complication of infection of the right lung than of the left; this is also true in a pleurisy. Chatard reports the findings in 31 of Osler's cases, in which pneumonia was right-sided in 13, left-sided in 5, and bilateral in 13. Of the 29 fatal cases, a pleurisy was present in 28, of which 13 were right-sided, 8 left-sided and 7 bilateral.

Undoubtedly a certain proportion complicating a pneumococcal pneumonia and pleurisy is due to the systemic infection, with a localization in the pericardium, and not necessarily the result of direct extension.

Pericarditis is frequently due to a tuberculous infection, associated with some clinical type of a tuberculosis. Clinically, the pericarditis may appear as the chief manifestation, but anatomically it is secondary to a tuberculous lung, pleura, tracheobronchial glands, a cervical adenitis, or it may be only the pericardial portion of a general polyserositis. A miliary tuberculosis of the diffuse or pulmonary type may involve the pericardium. A caseating tracheobronchial gland is relatively a frequent form of tuberculosis with pericarditis, especially in childhood and early adult life.

As previously indicated, a pericarditis may constitute only a portion of a more extensive anatomic involvement such as occurs in the various infections producing an infective endomyopericarditis—the pancarditis of von Jurgensen. It is this form of cardiac disease which is so frequently observed in early life; it is due to a rheumatic infection. The same condition may occur in the adult but it is due more frequently to a pneumonia, sepsis or gonorrhea.

Other forms of infection in the neighborhood of the pericardium may extend and result in a pericarditis.

Pleural empyema, a simple or suppurative mediastinitis, caries of the spine or ribs and pulmonary abscess and gangrene are occasional causes. Coronary occlusion due to thrombosis or emboli, particularly the infective variety, may be productive of pericarditis.

One of the cardinal and highly corroborative signs, in the diagnosis of coronary thrombosis, is the pericardial rub which, when present, is usually heard best over the left ventricle.

BACTERIOLOGY.—As pericarditis is most frequently only an incident or complication in the course of some other acute or chronic disease, the exciting organism will usually depend upon the primary form or focus of infection. The pyogenic cocci, pneumococcus, streptococcus, and the tubercle bacillus are the most frequent, but practically any organism may be present. In some of the acute infectious diseases or in the chronic wasting diseases, secondary infections occur and are responsible for the pericarditis. Terminal infections, with lowered resistance, are frequent and probably account for the relative frequency of pericarditis, irrespective of the primary disease.

For convenience of clinical description acute pericarditis may be subdivided into the acute plastic pericarditis and pericarditis with effusion.

The plastic character may predominate and little or no fluid exudate may be present, but more frequently the process gradually changes in form from a plastic type to one with an effusion—the two clinical types representing only a clinical and anatomic variation in the course of the same disease.

Clinical Varieties—ACUTE PLASTIC PERICARDITIS.—(I) *Symptomatology.*—(1) *Clinical History.*—There are no characteristic symptoms; in fact, not infrequently, all symptoms are wanting and the clinical recognition depends upon physical findings, or its existence is unsuspected during life and discovered only at autopsy.

(a) *Pain.*—The one and most suggestive symptom is pain, which may be of a dull aching character in the region of the heart, or it may be sharp, excruciating, and localized to the cardiac region or referred to the left shoulder and arm, not unlike the pain in an angina pectoris. In the course of some other acute infectious disease, discomfort or actual pain in the cardiac region should arouse suspicion of acute pericarditis and lead to a careful examination. When the pain is of the anginoid type, particularly with the dolor pectoris element without the angor animi, and when it is constant or prolonged, pericardial involvement should be suspected. In more than one instance, with these conditions present, a tentative diagnosis of acute pericarditis was made, even when the physical signs were yet uncertain.

(b) *Fever.*—Fever, like the pain, may or may not be present. In the infective type there is usually some elevation, as might be expected, but how much is due to the primary disease and how much to the complicating pericarditis is not easy or possible to determine. When present, the fever is usually moderate in amount except in the very acute or severe forms, depending upon the type of infection and the primary disease. The acute plastic pericarditis, so frequently encountered in the aged, or as a terminal manifestation, is usually fever-free.

(c) *Palpitation and Dyspnea.*—Palpitation and dyspnea are also extremely variable, frequently entirely absent, and more indicative of an associated valvular or myocardial lesion.

(2) *Physical Findings.*—(a) *Auscultation.*—The recognition of an acute plastic pericarditis usually depends upon a thorough physical examination and the detection of the characteristic, practically pathognomonic, auscultatory, to-and-fro friction rub; the “squeak of the leather of a new saddle under the rider” was first described by Laennec and ascribed to pericarditis, but later he changed his opinion. Subsequently, Collin, in 1824, again definitely declared that the “pericardial rub” is a sign of pericarditis, but he erroneously believed that it was produced by a dryness of the sac. The chief and determining characteristics of this pericardial rub are its great irregularity and variability, not only in rhythm but in time, intensity and audibility. The pericardial rub depends upon the rough, irregular surface of the pericardial areas, due to the fibrinous exudate and the cardiac action. In general, the friction rub is systolic and diastolic, corresponding to the cardiac cycle, but the sounds are not synchronous. The friction rub may accompany, precede

or follow the cardiac sounds; it is usually double, systolic and diastolic, but occasionally it is single or even triple and suggests an irregular shuffling sound. It may appear early in the disease, persist for a variable period or recur from time to time with subsequent examinations.

A few hours or minutes may suffice for it to disappear or reappear. More than once, it has been impossible to demonstrate in the clinic a pericardial rub which was present in the ward but a short time before. The very reverse is equally true. This variability may, in part, depend not only upon the amount and character of the exudate but, to a greater extent, upon the cardiac action and force. When doubt exists as to the presence of a rub, a few deep breaths or slight exercise, such as sitting upright or a change of posture, may suffice to intensify the findings and remove all doubt.

The rub may be audible over the entire precordia; perhaps it is transmitted beyond for a limited distance, but it possesses no definite line of transmission as in endocardial murmurs. Most frequently it is localized or heard with maximum intensity over certain areas, especially over the right ventricle, at the base, or at the apex of the heart. Intensity of the rub may be varied by the amount of pressure with the stethoscope.

(b) *Palpation*.—Palpation sometimes reveals the presence of a friction fremitus, but it is of relatively little assistance except in conjunction with auscultation. Inspection and percussion are negative in this type of pericarditis and reveal abnormal findings only if complications are present.

(II) *Diagnosis*.—Recognition of pericarditis in this type of the disease is rarely difficult. The pericardial rub is so distinctive, when once heard, that there can be no doubt. Conditions, however, may exist and render a diagnosis questionable or impossible. Lobar pneumonia, a chronic renal lesion with coma, acute cardiac involvement or some other disease, complicated with acute pericarditis, may so mask or obscure the physical findings that it passes unrecognized. This has occurred not infrequently, particularly in the pneumonia patients, when admitted in the terminal stage with rhonchi and large moist râles of pulmonary edema or failing compensation.

A pleuropericardial rub, due to a pleurisy, can usually be differentiated, as it is more definitely associated with the respiratory action than it is with the cardiac action; and it is heard with maximum intensity along the left border of the heart and lessens or entirely disappears when the patient suspends breathing. Further evidence of a left-sided pleurisy, plastic or with effusion, may be present and will be of assistance in the differential diagnosis.

When the pericardial rub is double, with maximum intensity over the base, and accompanying the cardiac tones, it may simulate or suggest a double aortic valvular lesion. Little or no difficulty need occur here in diagnosis, as an appeal to the peripheral vascular signs will at once render a decision possible.

A single systolic, pericardial rub localized at the apex may suggest a mitral regurgitation, but differential diagnosis is made possible by nega-

tive cardiac signs in pericarditis, and repeated auscultation will usually reveal lack of synchronism or an occasional double rub.

Reference should be made to the possible existence of a pericardial rub, due to a dryness of the sac in dehydrated conditions, as described by Pleisch in cholera, where no actual inflammation can be demonstrated. Admitting this possibility, there is no convincing proof that such is the case, while it is more plausible that the rub is due to structural changes, produced by infection or retained toxins.

PERICARDITIS WITH EFFUSION.—When the fibrinous exudate, in the acute plastic type, fails to undergo absorption or organization, an effusion may take place. Depending upon various factors the effusion or exudate may assume the serofibrinous, hemorrhagic or purulent form, the occurrence of which, in an acute plastic pericarditis, is so frequent that it is often designated as the second stage of an acute pericarditis.

(I) *Etiology.*—The same factors are present which are found in the acute plastic type. Rheumatism and rheumatic infections, pneumonia, tuberculosis and the septic infections should have special mention. The hemorrhagic form is not infrequently due to a tuberculosis, malignancy, aortic aneurysm, a chronic nephritis, or to the so-called hemorrhagic diathesis.

(II) *Symptomatology.*—(1) *Clinical History.*—As this form usually follows the acute plastic pericarditis, the onset and clinical course, in the beginning, is quite similar. In some the onset is slow, insidious, and without any complaint referable to the heart, even when the pericardium is enormously distended. Pain, fever, dyspnea and compression symptoms predominate and are the most important. In the developmental stage, pain and discomfort of the character encountered in the plastic form are present. As the fluid exudate increases, the pain usually decreases and dyspnea becomes more pronounced, although in individual cases the latter condition may be remarkably slight. At first the patient may rest best in the recumbent position, but as the dyspnea increases, he will insist on sitting upright or on leaning forward.

Distention of the cervical veins and cyanosis may be a marked feature associated with the dyspnea, being partly due to the exudate mechanically interfering with the cardiac function and partially due to the compression of the left lung in massive effusions.

The radial pulse is often irregular, soft and compressible, perhaps rapid and occasionally of the *pulsus paradoxus* type, although this is more constant in the obliterated form of pericarditis. Other compression symptoms consist of dysphagia, aphonia, cough, and pupillary disturbance such as are observed in aortic aneurysm.

(2) *Physical Findings.*—(a) *Percussion.*—The pathognomonic signs of pericardial effusion will be determined chiefly by percussion and auscultation. As the fluid exudate increases and distends the sac, the normal cardiac dulness gradually becomes altered, assuming an abnormal outline with changes in the cardiac sounds. Skoda has directed attention to the accumulation of the effusion in beginning pericarditis at the base of the heart, due to the less intimate contact, to the greater laxity of the sac

about the great vessel, and to the lighter gravity of the effusion as compared to the heart. Due to the limited space, distention of the cardiac portion of the sac occurs as the effusion increases. This may take place laterally, posteriorly, or in all directions, depending upon the amount of the fluid, and the resulting distention produces the physical signs characteristic of the disease.

Relatively early Epstein's cardiohepatic angle becomes dull; this condition was first described by Rotch. This may be increased by having the patient lean forward and to the right. Epstein also directed attention to the gradual change from a right angle to one more and more obtuse. When the distention is sufficient, the normal cardiac dullness is no longer present with the base directed upward but becomes pear-shaped with the base downward. This area of dullness is so characteristic of pericardial effusion that it is practically a pathognomonic sign.

Long ago Skoda called attention to the influence of change of position of the patient on the shape and boundaries of the area of dullness. The distended pericardium behaves very much like a partially filled rubber bag. When the patient is sitting upright, the base is increased; when leaning forward, the area of dullness is greater; while the lateral posture produces a shifting to the corresponding side. Shattuck more recently has described and emphasized the clinical importance of the same percussion findings.

With the distention of the sac, the pulmonary borders are pushed aside, particularly the left, with frequently a Skoda's resonance in the left axillary area.

Almost constantly, the lower lobe of the left lung presents evidence of varying degrees of compression as described by Bamberger, Ewart and Pins. This may be slight and limited to a small area below and to the inner side of the inferior angle of the left scapula, or the greater part of the lower lobe of the left lung is compressed, presenting physical signs suggestive of a pneumonia. This is usually designated as Bamberger's sign.

Localized dullness, with bronchial breathing, is usually present. In many instances the entire left lower lobe presents the findings suggestive of consolidation with the diagnosis of lobar pneumonia. Dullness, or even flatness, may be present over the posterior left chest from the interlobar fissure to the base. Bronchial or tubular breathing and bronchophony, usually without râles, are associated findings.

With these pulmonary signs, a careful examination should be made to determine the presence of a pericarditis with effusion. So suggestive are the findings that it has been possible, in several instances, to diagnose a pericarditis even before other pericardial signs were present or could be convincingly determined.

While the distended pericardial sac, with the resulting compression, is sufficient to produce the pulmonary signs, in some cases the findings are due to an accompanying pleurisy with effusion. This has been determined by puncture and aspiration of the pleural fluid, the compression

findings becoming less marked or disappearing entirely with removal of the effusion.

(b) *Auscultation*.—The auscultatory findings in pericarditis with effusion will vary with the stage of the disease. A rub can usually be detected before the effusion has become marked, but even then it is often audible over some circumscribed area of the pericardial dulness. In pleurisy with effusion, the rub disappears as the inflamed and fixed layers of the pleura are no longer in contact, but in pericarditis with effusion the conditions are different. The heart is relatively free, being suspended in the effusion, and when the myocardium has retained sufficient power, it is forced during systole through the fluid and comes in contact with the parietal layer of the pericardium. As the myocardium weakens or as the effusion becomes massive, the rub may no longer be heard. Detection of the rub is always of the greatest importance in the matter of diagnosis. Equally significant are the character of the cardiac tones and their gradual muffling or disappearance with subsequent examination. While as a rule the cardiac tones become less distinct as the fluid exudate increases, in not a few instances the tones remain loud and distinct throughout the entire course of the disease.

(c) *Palpation*.—Palpation, as emphasized by Skoda, may be of considerable assistance in determining the location of the apex beat in relation to the left border of the pericardial dulness. When present, it will be found well inside the area of dulness. Frequently, however, the location of the cardiac apex will depend, not upon palpation, but upon the determination of the point of maximum intensity of the cardiac tones by auscultation.

(d) *Inspection*.—Inspection is usually of but limited service, except perhaps in children, where a bulging precordia and obliterated intercostal spaces may be present.

Prominence in the epigastrium has been emphasized by some clinicians as an important sign, due, presumably, to an accumulation of fluid in the dependent part of the sac. Others have described a palpable left lobe of the liver from a downward displacement. Either or both may be present, but they can hardly be considered of much importance or regarded as early signs. Probably in many instances the epigastric prominence and palpable liver indicate a passive engorgement of the liver from failing cardiac compensation rather than a pericardial effusion.

It would be impossible to give more explicit or important information as to the method of observation and diagnosis than that given by Osler:

"In every instance, when a pericardial friction murmur has been detected, the practitioner should first outline with care—using the anilin pencil—the upper and lateral limits of cardiac dulness, mark the position of the apex beat, and note the intensity of the heart sounds."

(3) *Roentgenologic Examination in Pericarditis with Effusion*.—Roentgenologic examination may be of the greatest aid in confirming the diagnosis, or it may be of assistance in the differential diagnosis; it may also be a means of determining the relative amount of exudate. In any

doubtful case, the physical examination cannot be considered complete without the roentgenologic findings.

While the literature on roentgenologic examination and diagnosis in the various fields of medicine and surgery is sufficiently voluminous, relatively little applies specifically to pericardial disease. The recent investigations by George W. Holmes, as contained in his report, are very much to the point and furnish an excellent summary of the subject. Experimentally and clinically, various problems were investigated; this was

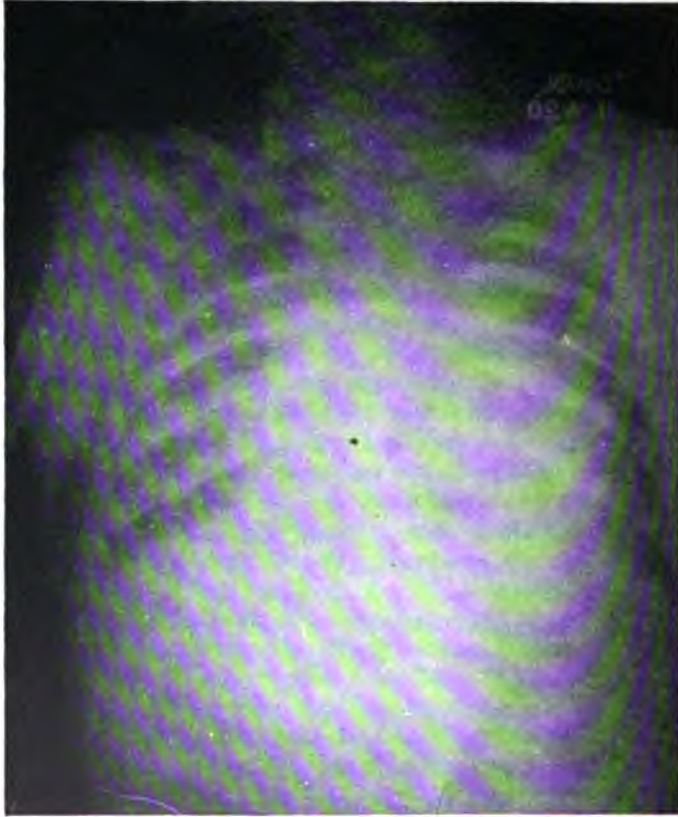


FIG. 1. RADIOGRAM OF PERICARDITIS WITH EFFUSION, DUE TO RHEUMATIC INFECTION.

particularly of service in the clinical diagnosis of pericardial effusion; following is a summary:

"In pericarditis with effusion, it seems to me that the findings may be grouped in the order of their importance as follows:

"1. An abnormally shaped heart shadow which changes with change of position of the patient. (So far as my observations go, this sign is not present in any other condition.)

"2. Obliteration of the normal heart outline.

"3. Change in shape of the angle formed by the posterior border of the heart, the diaphragm, and the spine.

"4. Faint or absent pulsation."

Years ago, Francis Williams recommended the examination of the patient in the sitting and recumbent positions, changing from the dorsal to the right and left sides, in order to determine any modification in the heart shadow. Examined in the upright position, the effusion produces



FIG. 2. RADIOGRAM OF PURULENT PERICARDITIS, SECONDARY TO SUPPURATIVE TUBERCULOUS CERVICAL ADENITIS.

the characteristic "pear-shaped" shadow and obscures the normal cardiac contour.

Diminution or obliteration of the cardiovertebral space as determined by vertical fluoroscopic examination is strongly suggestive of pericardial effusion, as cardiac hypertrophy and dilatation produce relatively little or no such change.

Transverse or oblique radiograms of the chest may be employed, either alone or as a part of the roentgenologic examination.

Absence of pulsation speaks strongly for effusion, although in limited exudates a slight transmitted pulsation may be present. In widely dilated, decompensated hearts, there may be little or no pulsation, but the outline of the shadow, lack of influence on change of position, and difference in the angle formations will assist.

Williams, Holmes, and others are all practically agreed that it is impossible by roentgenologic examination to determine the character of the effusion.

(III) *Diagnosis*.—The recognition of a pericarditis with effusion is not difficult, if the case has been under observation from the onset, and there have been the necessary care and repeated examinations. If examined for the first time, when the effusion is already present, particularly when complicating some other disease, pericarditis is often overlooked or misinterpreted. This is abundantly proved by the autopsy records in any hospital with a sufficient amount of material.

Undoubtedly the greatest difficulty and the largest number of mistakes occur in the differential diagnosis between a pericarditis with effusion and cardiac dilatation. Theoretically this is easy; any senior student or member of a hospital quiz class can readily give a complete list of differential points, but, when applied clinically, there exists a wide difference filled with difficulty.

A recapitulation of the physical signs, which should be of service, may be made as follows:

1. The triangular, "pear-shaped" area of dulness, with the apex directed upward, speaks for pericardial effusion.
2. Visible, palpable or auscultatory apex beat inside the area of dulness has the same significance.
3. Gradually diminishing intensity, muffling or absence of the heart tones indicate effusion, unless the myocardium is greatly weakened. In dilatation, the tones are sharp and distinct; the rhythm is often disturbed.
4. A comparatively strong radial pulse, with a weak apex beat on palpation and muffled, indistinct heart tones on auscultation, is suggestive of effusion rather than a dilatation.
5. A pericardial rub, even transitory, over any portion of the area of dulness is a most important finding in favor of pericarditis.
6. Rotch's sign, dulness in the cardiohepatic angle, is of value when combined with other findings.
7. As described by Epstein, effusion produces an obtuse cardiohepatic angle, while cardiac dilatation produces a right angle.
8. Compression of the lower lobe of the left lung, producing Bamberger's sign, is almost always due to effusion. Only very rarely does it result from cardiac dilatation, as determined at autopsy.
9. Visible cardiac impulse is usually absent in effusions and present in dilatation.
10. Palpatory impulse and shock of the cardiac sounds occur more frequently in dilatation.

11. Roentgen examination is often of the greatest service.

12. In doubtful cases, the exploratory puncture will eliminate any question of doubt.

Even after the most careful physical examination, a definite diagnosis may not be possible until exploratory puncture is made. A differential diagnosis between pericardial effusion and cardiac dilatation has been one of the most difficult clinical problems; in many instances where effusion was suspected, only a dry puncture was obtained.

Left-sided pleurisy with effusion, displacing the heart to the right, will cause but little difficulty when the signs are carefully determined. Usually the two diseases are sufficiently distinct and little or no confusion exists.

Pneumonia with pericardial effusion presents far greater difficulty, not only in determining its presence but in estimating the amount of the fluid. Generally there is a far greater quantity than is suspected, as the pleuropneumonia prevents or interferes with any accurate estimate.

CLINICAL VARIETIES OF ACUTE PERICARDITIS.—*Pericarditis Sicca.*—This type is a dry, plastic, fibrinous pericarditis, characterized anatomically by a predominance of the fibrinous exudate which may be circumscribed or diffuse; it is clinically manifested by symptoms as previously described and by the pathognomonic physical sign—the pericardial rub.

Serofibrinous Pericarditis.—This is the most frequent form of pericarditis with effusion, occurring usually as the second stage of a dry pericarditis; it is generally secondary to rheumatic infections but occasionally it develops as a primary lesion.

Purulent Pericarditis.—This form may occur secondary to the plastic or serofibrinous type, the exudate gradually changing to the purulent type. More frequently it develops in the course of some pyogenic infection, as a sepsis, pyemia, pneumonia, or some focal infection.

Hemorrhagic Pericarditis.—In this form, the effusion is mainly a blood-stained serum containing little fibrin and only a few leukocytes. Its presence usually indicates a tuberculosis, malignancy, chronic Bright's disease, or some blood dyscrasia with a hemorrhagic tendency.

Tuberculous Pericarditis.—This form is due etiologically to an infection of the pericardium with the tubercle bacillus; it usually occurs as a complication in the course of a previous infection of some of the other organs, but it may be primary. Tuberculous pericarditis is capable of producing quite a variety of anatomic changes, some of which are characteristic. The exudate varies from a fibrinous, serofibrinous or hemorrhagic to even a purulent form, such as occurs in other types of infection. Careful search will often reveal the presence of tubercles or a caseating lesion in proximity to the pericardium, *e.g.*, a tracheobronchial or mediastinal gland. It has been observed at all ages but perhaps more frequently during childhood or early adult life, coincident with the prevalence of infection in the other organs, such as the glands, lungs and pleura. The symptoms and signs are those of an ordinary simple pericarditis and only the latency, the associated clinical disease, or the obtaining of a bloody

fluid on puncture may first suggest the tuberculous origin. Complete laboratory examination, including cultures and inoculations, of the aspirated fluid may furnish valuable diagnostic assistance.

Syphilitic Pericarditis.—With the recent development in the knowledge of syphilis and its etiologic significance in cardiovascular disease, involvement of the pericardium might be considered as a not infrequent occurrence. However this may be, syphilitic pericarditis, at least up to the present, presents more of an academic interest than of a real clinical entity.

The increasing frequency with which the *Spirochaeta pallida* is demonstrated in cardiac and aortic lesions would justify the conclusion, or at least give reason for strong suspicion, that the pericardium must also become infected. If it escapes, there may be something in the type of the infection or structure of the pericardium, as the scant vascularity, which renders a relative immunity. Ricord, in 1851, first described the disease; Virchow, ten years later, in 1861, reported the second case. Infection of the pericardium probably occurs soon after the initial lesion, during the period of systemic infection, and it is followed by a chronic process which results in a plastic exudate and adhesions. Gummas of the sac have been described but are relatively rare; a serofibrinous type of the disease is also rare.

CHRONIC PERICARDITIS.—In some instances in which there is a mild onset, slight symptoms and a prolonged clinical course, a designation of chronic pericarditis appears justifiable, particularly when accompanying such diseases as carcinoma, tuberculosis, diabetes or chronic nephritis.

Acute pericarditis is often followed by a prolonged convalescence; the acute symptoms gradually disappear, while the physical signs still persist. Chronicity may justly arouse suspicion of a tuberculous pericarditis of a mild unrecognized suppurative type, or of the development of an adhesive pericarditis.

Treatment.—This must necessarily depend upon the form of the disease, the stage of development, the predominating manifestations, and the existing complications. It can hardly be claimed that there is any means at our command to prevent infection of the pericardium. The appropriate therapeutic treatment for the various forms of infection enumerated in the etiology is a matter of fact. Whether the salicylates or similar treatment for a rheumatism have any definite influence in preventing a pericardial complication is open to question. It might seem reasonable to believe that the longer the arthritis continues, the greater the danger of complications. While there may be a question on this point, there can be little doubt as to the beneficial effect of **absolute rest** as a preventive measure; this measure is well known and recognized in the prevention of acute endocarditis. Prolonged, absolute rest, not only in acute rheumatism, but in many other acute infections, may be of greater service than can be actually estimated.

When the pericarditis is already present, the therapeutic indications consist in the following: (1) giving the patient relief; (2) combating the inflammation; and (3) preventing the cardiac failure.

Pain and dyspnea, the predominating symptoms, may be sufficient

to demand immediate relief. If mild or moderate in severity, the application of an **ice bag** or **ice coil** may suffice. Some patients will prefer the use of a **hot-water bag** or **electric pad**, but, therapeutically, the application of cold is to be preferred. When the discomfort is pronounced or extreme, **opium** or one of the **opiates** will give relief; these measures may require repeating as indications demand.

As to the second indication, we are almost as helpless as in the efforts to prevent the infection. Rest, with the application of the ice bag or coil will be of some service. Many of the methods and drugs recommended are very questionable, more empiric than rational. When one recalls the varied etiology and anatomic changes, it would be hoping for the impossible to expect a cure or even an improvement in certain types, no matter what treatment might be employed. Counter-irritation blisters, antiphlogistics and resolvents, formerly so strongly recommended, have fallen into discredit and find no place in the treatment of pericarditis, unless it be in the stage of effusion. Even then, the beneficial effect is so doubtful as hardly to merit recognition or sanction. The salicylates, alkalis, quinine, atropine, iodides and a long list of other drugs belong in the same category.

In the rheumatic form of pericarditis, **sodium cacodylate**, hypodermically or intravenously, to full therapeutic effect, is apparently of real value. Repeated use, over a considerable period, has only strengthened the conviction of its efficiency.

The third indication, prevention of cardiac failure, involves several considerations. The main objects to be attained consist (1) in minimizing or removing the mechanical hindrance to the cardiac action—the removal of the pericardial effusion, and (2) in limiting the damage to the heart and reinforcing the myocardium.

Just what factors control the production of an effusion and how they may be influenced or governed, it is impossible to say. The slowing of the heart, due to rest and application of cold, must have a beneficial effect in several ways. The myocardium is subjected to less strain, its contractile power is increased, and the decreased activity must assist in minimizing the tendency to myocarditis, as well as in decreasing the irritation of the inflamed pericardium.

Fortunately the pericardium is readily distensible, permitting a considerable accumulation of fluid before there is sufficient pressure to interfere with the cardiac function. In most cases, watchful expectancy is all that is necessary, as the fluid will gradually disappear. As a matter of fact, little or no result may be had from various therapeutic efforts, short of surgical means. Rest in the **semiprone** or **sitting position** to relieve the dyspnea, **free elimination**, and **regulation of the diet** are only general measures, dictated by common sense. As for any specific drug therapy, there is none.

When the heart is embarrassed mechanically by pressure of the fluid, **surgical relief** by **aspiration** or **drainage** is necessary. The indications and methods will be described in a subsequent section.

A few statements should be made in reference to the efforts to support the failing heart. Opinions are at variance in the use of digitalis in any form of pericarditis. With due regard and respect to those opposed, **digitalis** has been used with apparent benefit, in both the dry and effusive forms. As in valvular disease, the beneficial effect has been more marked with a rapid, irregular heart. **Strychnia**, as a general muscular stimulant, has been of much service. In acute cardiac disturbance such remedies as **camphorated oil** and **caffeine sodium benzoate** should be used.

PARACENTESIS PERICARDII.—**Puncture** of the pericardium may be done either as an aid in diagnosis or for therapeutic purposes. In all doubtful cases, **exploratory puncture** is strongly recommended. Performed with due care, under aseptic conditions, no harm can be done. **Repeated punctures** in the same case may be indicated. By means of the puncture, not only the presence or absence of fluid, but its character, will be determined. It is only by this means, in not a few instances, that a final and absolute diagnosis may be made. This statement applies generally, but specifically to the question of cardiac dilatation and pericardial effusion. More than once, after a puncture, it has been necessary to revise a diagnosis of effusion to cardiac dilatation or *vice versa*.

Obtaining fluid is the best evidence of pericardial effusion and affords the opportunity of further examination by laboratory methods and animal inoculation. As for the **therapeutic puncture**, this is a clinical problem, often most difficult to decide. Certain indications were given by Schuh and Skoda as follows:

1. The vital indications, when the life of the individual is threatened by cardiac failure or dyspnea.
2. When the effusion fails to absorb after prolonged observation, in cases in which other means have produced no effect.

The site of the puncture is not a matter of indifference, as failure may occur or harm may be done. Gumprecht mentions the following considerations:

1. Select a point in the location of the pericardium as determined by the examination.
2. The location of the internal mammary vessels should be avoided.
3. No harm should be done to the pleura.

Not only are these considerations important but also the location of the heart in the pericardial effusion. Skoda was of the opinion that the heart sinks downward in the fluid, because of its greater density. According to the findings of Schaposchnikoff the very opposite is true, *i.e.*, the heart floats in the fluid unless the aorta is weakened and elongated by the inflammatory process. This view was accepted by Romberg, Doeberl, Fraenkel and others.

The accompanying illustration will show the various sites which have been selected and recommended for exploratory puncture or aspiration. Everything considered, it would seem that the fifth intercostal space, in-

side of the line of dulness not far from the normal location of the apex beat, is the site to be preferred. In this area, the distended pericardial sac is in close contact with the chest wall, the pleura is pushed aside and if the heart is in contact with the pericardium, little or no harm can be done, as the underlying thick left ventricle is not easily damaged. The author can vividly recall his first puncture in a questionable pericardial effusion or cardiac dilatation. Under the direction and supervision of the attending physician, the needle was inserted in the right fifth intercostal space, close to the sternum. Contrary to expectations, no pericardial fluid was obtained but there was an active spurting of blood; a cardiac,

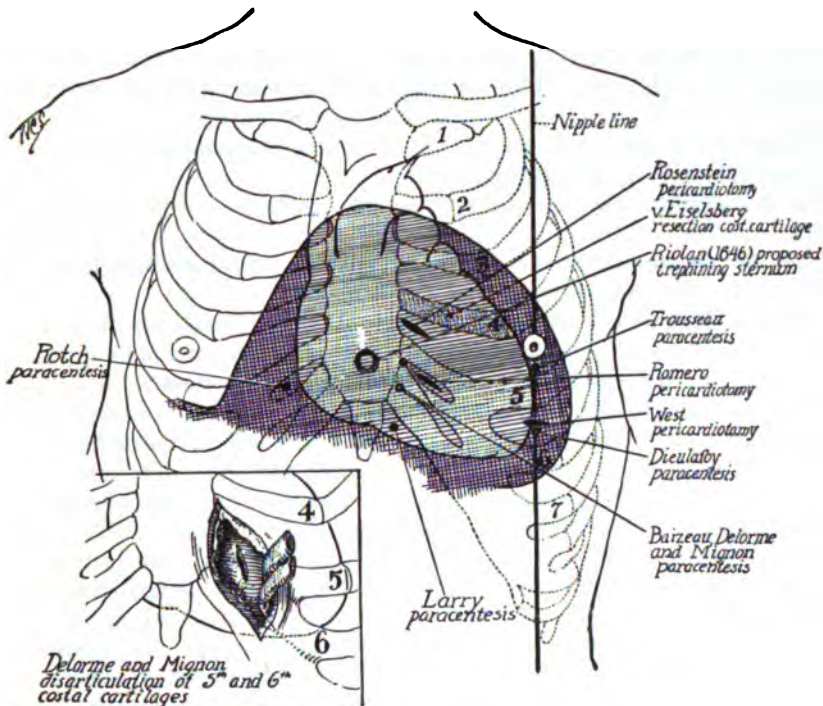


FIG. 3. DIAGRAM GIVING THE MORE FREQUENT SITES OF ELECTION IN PERICARDIAL PUNCTURE, ASPIRATION AND DRAINAGE.

as well as a pericardial puncture had been made, fortunately without any bad results. With the usual and necessary precautions, this could hardly occur when the puncture is made in the normal apical region.

In most cases, with the usual physical signs, when puncture is indicated, the site of election is the left fifth intercostal as described. When compression signs are pronounced, and doubt exists as to the diagnosis between a simple compression, lobar pneumonia or coexisting left-sided pleural effusion, the puncture has been made posteriorly in the eighth or ninth interspace, just below and inside the angle of the scapula. If a pleural effusion is found, this should be aspirated and the effect on the

symptoms and signs determined. When no pleural fluid is obtained, the needle may be inserted deeper until the pericardium is punctured and then aspirated. After removal of the fluid, compression findings decrease or usually disappear, but if a pneumonia exists, emptying of the sac has no appreciable effect on the pulmonary signs. On a number of occasions the same procedure was employed after removing the fluid in a pleural effusion. The posterior puncture should not be made if there is any suspicion that the pericardial fluid is purulent, if compression signs are absent, or if there is no question as to pleural or pulmonary pathology.

As soon as the nature of the fluid is determined, the further course of procedure is variable. Serofibrinous or hemorrhagic exudates should be aspirated, and as much removed as possible. To assist the flow, the patient may be in a sitting, semi-sitting or lateral position and the fluid removed by siphonage. Usually moderate suction with an aspirating apparatus will be found more practical, and oftentimes it is absolutely necessary for a successful result. Therapeutic pneumopericardium may be done, depending upon the indications.

If the exudate on exploratory puncture is found to be purulent, incision and free drainage should be done at once. The same treatment should be employed in protracted, recurring effusions which fail to respond to simple aspiration.

Course, Duration and Termination.—No definite and absolute statement is possible, as the determining factors are too variable. Approximate accuracy may be attained in reference to the course in acute pericarditis, as the plastic type generally becomes changed into a pericarditis with an effusion. The primary disease, of which the pericarditis is only a complication, is often a far more important factor in determining the course, duration and termination than the pericarditis. The plastic pericarditis is usually of short duration, from a few hours to a few days, terminating in recovery or in a pericardial effusion which may run a clinical course of weeks or months. When the plastic exudate is limited, it may undergo absorption and the pericardium return to normal. The so-called "milk-spots" or "soldier-spots" on the heart, so frequently found at autopsy, may be due to a sclerotic thickening of the visceral pericardium, the remains of a previous pericarditis. Almost without exception, the exudate undergoes organization and produces adhesions or obliteration of the sac. When effusion occurs, after a varying period, the fluid is gradually absorbed and the fibrinous portion becomes organized with the pericardial layers adherent. Under the heading of Morbid Anatomy, reference is made to some of the factors and possibilities in pericardial exudates. The end-results in the various forms of acute pericarditis will be described under Adherent Pericardium.

Prognosis.—The prognosis is variable and questionable, depending in part upon the form of the disease, but far more upon the primary disease and the associated pathology. Acute plastic pericarditis, uncomplicated, is never fatal.

The immediate outlook in the serofibrinous form, particularly of the rheumatic type, is favorable; the ultimate outcome, due to cardiac in-

volvement or to the resulting adhesive pericarditis, is often unfavorable.

Myocarditis is practically always present, either as an accompanying cardiac involvement of the same infection, or by extension from the pericarditis. Purulent pericarditis of septic origin is usually fatal, often within a few hours or days. The tuberculous form presents a somewhat better outlook, occupying a prognostic position somewhere between that of the dry plastic and the purulent types.

Pericarditis tends to a fatal termination in the following ways: (1) by mechanically interfering with the cardiac action by the pressure of the effusion or the obliteration of the sac by adhesions; (2) by extension of the inflammation producing a myocarditis; and (3) possibly through the injurious effects from absorption of the toxins. The first-mentioned effect is the most dangerous, although the presence of a myocarditis is a serious matter.

After all, a prognosis most carefully determined, based upon all the existing findings, may be upset by the course of the primary disease or by some unforeseen complication, such as an acute endocarditis or embolism.

Morbid Anatomy.—The anatomic changes in a pericarditis are variable, depending upon the exciting organism, as well as upon the local and general resistance. Following the infection, the pericardium becomes lusterless and a leukocytic infiltration occurs, followed by a varying amount of fibrinous and fluid exudate. The exuded fluid is relatively rich in fibrinogen, which undergoes subsequent changes and determines the character of the exudate. Opie is of the opinion that the fibrinogen is acted upon by a proteolytic enzyme, derived mainly from the polynuclear leukocytes. In the presence of the ferment, a fibrinous exudate is formed; when the ferment is absent, the exudate remains fluid. If the organisms are particularly numerous and the leukocytes are abundant, the ferment digests the fibrin and the exudate becomes purulent.

Plastic pericarditis, the usual and most frequent form, may be local or general. As the exuded fluid and leukocytes are given off from the circulation, the fibrinous formation will first appear in the course of the vascular supply of the pericardium and heart. Later the entire surface becomes covered and, when abundant, forms a fibrinous layer with an irregular surface and long shreds—the shaggy heart or *cor villosum*. The appearance of the pericardium in this form has been compared to that of two pieces of bread and butter pulled apart. The pericardial surface may be covered with a thin uniform layer, but more frequently there is a ridge and furrow formation, due, according to Kornitzer, to the rotary action of the heart during systole.

The plastic form of pericarditis is characterized anatomically by the abundance of the fibrinous exudate, with little or no fluid. After a varying period of hours or days there is an accumulation of fluid, producing a pericarditis with effusion. The rapidity of formation, as well as the amount and the character, is variable.

Occasionally a dry form becomes converted into one with effusion

with surprising rapidity—within a few hours, and usually within a few days at best. The amount may be limited to a few cubic centimeters, usually from 2 to 300 cc. (32.4 minims to 10.14 fluidounces), but it may reach or even exceed 2 liters (4.227 pints). At autopsy, Verney removed 4000 cc. (135.24 fluidounces).

The type of effusion most frequently encountered is the serofibrinous, associated with the rheumatic infections. Less frequently the fluid is hemorrhagic or purulent.

It should be emphasized that an inflammatory involvement is rarely, if ever, strictly limited to the pericardium. The underlying myocardium presents evidence of infection, perhaps only the most adjacent portion, but more frequently it is extensive, involving the greater part, as well as the endocardium—a pancarditis.

The fluid may become sacculated by the fibrinous exudate or adhesions, so that the greater part is found walled off and limited to some particular portion of the pericardium. Multiple pockets may form, particularly in the process of absorption and organization.

Adhesions may form, either cordlike or more extensive, binding together the two layers of the pericardium. This is more frequent in the later stages of the disease, but during the acute and early stage the layers are partially or completely adherent; this is due to the inflammatory exudate.

Pathologic Physiology.—The heart, under normal conditions, is suspended at the base by the great vessels, hanging practically free in the pericardial sac. According to Adamkiewicz and Jacobson the normal intrapericardial pressure varies from -3 to -5 mm. Hg. Although the serofibrinous structure of the pericardium is such as to permit of considerable stretching, the support given to the heart is of great physiologic consideration in maintaining a normal circulation. When involved in some inflammatory process, the sac is weakened, more easily stretched and the normal support lessened. In the event of a pericardial effusion, the resulting intrapericardial pressure is exerted not only upon the sac but also upon the heart. The distensibility of the pericardium is of greater importance than the actual amount of contained fluid, so far as symptoms and signs are concerned.

Experimentally François-Franck, Cohnheim, Starling and others have determined by injections into the dog's pericardium, that from 20 to 30 cc. (5.42 to 8.11 fluidounces) of oil raised the pressure in the vena cava, while that in the aorta and pulmonary vein was unchanged. When an additional 10 cc. (2.71 fluidounces) or more was injected, there was produced a sudden fall in the pressure, both arterial and venous. As soon as the intrapericardial pressure exceeds that in the vena cava, the auricles collapse, and the ventricles, failing to receive a sufficient supply of blood, can no longer maintain a normal pressure in the aorta. If the intrapericardial pressure be maintained, cardiac failure will soon occur, but if a small amount of the fluid be removed, the blood pressure and circulation are rapidly reestablished.

In pericarditis, with effusion, the very same thing occurs, with this difference, that in pericarditis the pressure of the effusion is exerted upon the abnormal tissues of the heart and pericardium.

ADHERENT PERICARDIUM

Synonyms.—Adhesive pericarditis, obliterated pericardium, synechiae pericardii, concretio pericardii cum corde and chronic mediastino-pericarditis are all synonymous with adherent pericardium.

Definition.—Adherent pericardium, as the term indicates, is a condition in which the sac is partially or completely obliterated by adhesions. It cannot be considered as a primary clinical entity, as it is always secondary to some previous pericardial disease, usually some form of pericarditis. The clinical symptoms and signs are not due to the obliterated sac alone but result from the associated pathology, the symptom-complex of which is sufficient to give it special consideration and by which an adherent pericardium is recognized.

Etiology.—In the greater number of instances, it is secondary to pericardial disease, particularly pericarditis of any form. Every type of infection or disease capable of producing inflammatory involvement of the pericardium must be considered as an etiologic factor. The most frequent and important are rheumatism, pleuropneumonia and tuberculosis. In some instances the primary disease is mediastinal, such as mediastinitis, an aneurysm or malignant involvement. As regards age, it occurs more often in childhood and early adult life, as might be expected, since it follows in the course of pericarditis.

Symptomatology.—Adherent pericarditis presents no characteristic clinical picture. With such a varied possibility in the morbid anatomy, there could scarcely follow any fixed or regular chain of symptoms. For convenience of description, the cases may be subdivided into the following: (1) silent group; (2) those presenting the symptoms of chronic heart disease; and (3) those with Pick's syndrome—pericardial pseudo-cirrhosis.

1. When the adhesions are purely intrapericardial, no symptoms are present, the condition is unrecognized clinically and can be determined only by autopsy. The pericardium is so loosely attached, the mobility so great, that partial or complete obliteration produces no symptoms. The only possible exception, as previously mentioned, that may occur, is when the fibrous bands constrict the vessels at the base of the heart. Even this must be extremely infrequent and probably productive of but slight, if any, symptoms.

2. The usual manifestations of adhesive pericarditis are those of a chronic heart disease, not due primarily to the adhesions, but to the associated cardiac pathology. Precordial discomfort or actual pain is fairly common and may be due to a subacute inflammation in the sac, in the adjacent pleura or in the mediastinum. Palpitation, dyspnea, cough and systemic disturbances are the rule.

The most frequent associated cardiac lesion is a myocarditis; this is practically always present. Valvular disease of some form ranks next in order of frequency.

It should be emphasized that the clinical phenomena of adherent pericarditis are in no way characteristic, that the associated cardiac pathology is responsible for the symptoms in the earlier stages, and the effect of the adhesions becomes manifest only when the traction is sufficient to interfere with the compensation. Extensive fixation of the pericardium may occur without clinical symptoms. Temporary disturbance of compensation may follow some physical exertion or prolonged cardiac strain.

3. Pick's syndrome consists of an ascites, with an enlarged, firm liver, but without any edema of the legs.

PHYSICAL SIGNS.—*Inspection.*—As might be inferred from a consideration of the morbid anatomy and clinical symptoms, the intrapericardial type of adhesions produces no physical signs. Clinical and physical phenomena occur only when the obliterated sac is associated with adhesions binding it to the surrounding tissues. When this occurs, various signs may be present, many of which are determined by inspection.

Systolic retraction of the chest wall, particularly in the lower precordial region, is the most important single sign. The retraction may be only slight, limited to one or two interspaces; sometimes the costal cartilages and epigastric region, as well as the interspaces, are decidedly drawn in with each cardiac contraction. Retraction of the interspaces does not possess much diagnostic value, as this is often present in large dilated hearts or in obliterated pleuropericarditis without an adherent pericardium. Even in health this may be observed over the upper precordial area; perhaps it is the expression of marked mobility of the heart and failure of the lung to fill in the space.

In aortic regurgitation, it is common to observe systolic retraction of the lower precordial interspaces, due to atmospheric pressure compensating for the great reduction in the size of the heart and intrathoracic pressure during systole. The same phenomenon may exist in cardiac dilatation from any cause. Adhesions between the pericardium and chest wall due to a pleuropericarditis may produce intercostal retraction, synchronous with the heart's contraction from the cohesion within the normal pericardium. When the ribs, costal cartilages, perhaps lower sternum, as well as the intercostal spaces, are retracted, the significance and conclusion indicate an adherent pericardium.

Skoda called attention to systolic retraction of the apex beat as a sign of importance. Subsequently this was brought into question by Traube, Riegel, Friedreich and others, mainly on the undetermined physiologic ground as to the manner of contraction of the heart. Skoda was of the opinion that, during contraction, the heart decreases not only in the transverse diameter but in the longitudinal as well. However this may be, physiologically, in adherent pericarditis with adhesions between the apex and chest wall, a systolic retraction of the apex beat still remains a valuable clinical sign.

Perhaps the next finding in the order of importance is the diaphragm sign of Walter Broadbent. When adhesions exist between the pericardium and diaphragm, the cardiac tug is exerted on the thoracic attachment of the diaphragm, with a visible retraction of the intercostal spaces. This is best observed between the eleventh and twelfth ribs on the left side posterior. Broadbent's sign is usually considered of much clinical value but is not pathognomonic. The same phenomenon may be observed occasionally in large hypertrophied hearts, where no pericardial obliteration is present. Sir William Broadbent has directed attention to the failure of the diaphragm to descend during inspiration, when its activity is restricted by adhesions to the heart.

At least two of the peripheral signs are determined by inspection of the cervical region. Friedreich's sign, a diastolic collapse of the cervical veins, is due to a sudden emptying of the vessels as the right heart rapidly dilates from the traction of the adhesions, following the tension during systolic contraction. The more extensive and firm the adhesions, the more pronounced the diastolic collapse; in some instances it is so complete that the vessel is not only collapsed but the overlying tissues appear depressed.

Kussmaul's sign is an inspiratory swelling of the cervical veins, occurring at the height of inspiration and resulting from mechanical interference with the venous flow from the stretched adhesions about the base of the heart.

Palpation.—Under normal conditions, according to the laws of gravity, the heart will shift from side to side, with change of position of the individual. This is always more marked to the left. With adhesions between the heart and chest wall, the apex on palpation is fixed. Fixation of the apex does not however signify pericardial adhesions, as the cardiac mobility may be limited by a pleural effusion, pulmonary consolidation, neoplasm or some other conditions. Palpation may detect a diastolic rebound at the apex, produced by the cardiac impact from the traction of the adhesions at the beginning of diastole. When present it is probably the most valuable single sign and by many clinicians is considered pathognomonic; but unfortunately it is not a frequent finding.

Percussion.—Percussion usually reveals a much increased cardiac dullness, increased from the associated cardiac pathology and the indurative mediastinopericarditis. Of far greater importance is the absence of the respiratory excursion along the borders of the area of heart dullness, which is fixed and fails to move with respiration or change of position. Some mobility and respiratory excursion may be present, even though adhesions exist. Pulmonary emphysema not infrequently interferes with the determination.

Auscultation.—On auscultation, it is usually possible to detect cardiac murmurs due either to an endocarditis or a myocarditis. In the advanced stages, with cardiac dilatation and a failing heart, a systolic murmur is practically always present. These findings can hardly be considered indicative of pericardial adhesions. Occasionally there may be heard at the apex auscultatory findings of real value. Instead of the

coupled first and second tones, three sounds are audible, with the accent on the last. This accentuated sound is synchronous with the palpatory rebound of the apex and possesses the same etiologic and clinical significance.

Pulse.—*Pulsus paradoxus* of Kussmaul, in which the radial pulse during inspiration becomes small and weak, sometimes imperceptible, may be present. While usually described as one of the findings in adhesive pericarditis, it possesses but little diagnostic value either as a sign of adhesions or a pericarditis. Its presence is of relative value when associated with the other physical findings indicative of pericarditis.

Other Physical Signs.—Other physical signs, more or less important, may be present and, combined with the findings already described, will assist in filling out the clinical picture. For completeness, a few of these should be mentioned. Skoda emphasized a prominence of the precordia as a sign of pericardial adhesions when an effusion could be excluded. Like some of the other findings, this is more valuable as indicating a cardiac hypertrophy. Marked increase of the cardiac impulse, often undulatory in character, beginning at the base, may be observed.

Tuczek and Riegel have described a finding which they consider important as indicating the presence of even limited adhesions. During inspiration, the normal apex beat becomes weaker; during expiration it is stronger. If pericardial adhesions are present, the apex findings are reversed—stronger during inspiration and weaker during expiration.

Perez's sign consists of a creaking sound on auscultation over the sternum when the patient elevates and lowers the arms, produced, presumably, by the movement and friction of the mediastinal adhesions.

Pick's syndrome, while primarily an adherent pericardium, produces chiefly abdominal and hepatic symptoms, more suggestive of a cirrhosis. The condition is usually described along with the other forms of liver diseases, and for further description the reader is referred to that section.

ROENTGENOLOGIC EXAMINATION.—By this method no assistance can be had in the simple intrapericardial type. Much information may be obtained by fluoroscopic and film examination when the obliteration is accompanied by external pericardial adhesions.

Fluoroscopy is particularly important as this will give definite information as to the size and outline of the heart shadow, and will also aid in determining the mobility of the heart and diaphragm. Fixation of the heart and diaphragm by adhesions is, probably, the most important finding, but does not, of course, necessarily indicate an obliterated pericardium. Simply by indirect inference, detecting the associated secondary pathology of adhesive pericarditis, one is justified in concluding that the initial lesion is also present. This becomes more certain or an actual reality when the fluoroscopic findings, the clinical history and physical signs are correlated. Roentgenograms are also of service but will fail to furnish any additional information; in fact, not as much as the fluoroscope, unless multiple plates be made with the patient in various positions. When this is done, the cardiac fixation as well as pleural or diaphragmatic adhesions may be determined. Repeated

roentgenologic examination of patients with pericardial effusions, during convalescence, often reveals considerable enlargement of the cardiac shadow. The same finding is frequently observed in adhesive pericarditis, the shadow apparently exceeding the area of dulness on percussion. This discrepancy may occur, due to inability to outline the heart dulness in the presence of an emphysema or perhaps from the accompanying indurative mediastinitis.

Suppurative pericarditis, either pyogenic or tuberculous, occasionally results in a calcification of the sac and its contents. It may be partial or complete, usually without symptoms and first detected at the autopsy but occasionally diagnosed by means of a roentgenologic examination.

ELECTROCARDIOGRAMS.—The shifting and rotation of the normal heart, on change of position from side to side, produces a recognizable change in the height and conformity of the QRS wave, usually present in all three leads but most marked in leads I and III. In obliterated pericarditis, with fixation of the heart, shifting of the electric axis is absent.

Diagnosis.—It would be difficult to select many, if any, diseases presenting a greater range of diagnostic possibilities than may be encountered in adhesive pericarditis. The variations are so great as to be quite sufficient to satisfy the most exacting. From a symptom-complex with an easily determined diagnosis, there are varying degrees of manifestations and diagnostic certainty, even to the vanishing point. The diagnosis may be relatively easy, when there is an accurate history of infection with cardiac symptoms, and when the patient has been under observation and carefully examined, finally developing the clinical picture as already described. Perhaps no single sign is sufficient as a basis for diagnosis, but the symptom-complex is clear and decisive. Mistakes in diagnosis are rather ones of omission than misinterpretation. Too often the possibility of pericardial involvement is entirely ignored. The usual symptoms are those suggestive of cardiac disturbance with associated physical findings and diagnosed as valvular or myocardial disease. If there is a good clinical history obtained from the patient or previous medical attendant, and a careful thorough physical examination is made, there should be no ground for doubt or mistake. There may, however, be mitigating circumstances, some valid reason for excuse, when the patient is examined for the first time, without any obtainable history and perhaps with the heart in broken compensation. At the best, only a tentative diagnosis can then be made.

The differential diagnosis is usually most concerned with aortic regurgitation or with a cardiac dilatation from any cause. The confusing similarity consists in the local cardiac signs, the enlarged area of dulness with the systolic retraction of the intercostal spaces and perhaps slight retraction of the costal cartilages. When in doubt as to an aortic regurgitation, an appeal to the peripheral circulation will at once render a decision possible.

Dilatation of the heart often presents greater difficulty in differentia-

tion and sometimes constitutes an actual impossibility, particularly when the dilatation is due to a failing heart secondary to an adherent sac. Besides the increased dulness and systolic intercostal retraction, cardiac dilatation is capable of producing Broadbent's sign, the existence of which usually arouses the suspicion of adherent pericarditis. Dilatation of the heart, besides failing to present other evidence of pericardial obliteration, is usually associated with some cardiac, renal, vascular or pulmonary disease.

What has been said in reference to mistakes in diagnosis applies particularly to the recognition of Pick's syndrome, pericardial pseudocirrhosis. The attention is centered on the liver and abdominal phenomena to the exclusion or neglect of other possibilities.

Treatment.—**MEDICAL.**—The therapeutic indications are to prevent the formation of the adhesions and to combat the effect when once produced. Unfortunately, there is no course of procedure that will insure a return of the pericardium to normal when once involved in a pericarditis. The measures as outlined in the management of the acute stages may be of some service—how much cannot be stated. Drug therapy is practically of no service; much more may be accomplished by nonmedicinal measures. Carefully regulated **exercise** and **diet**, with good **elimination**, are all important. Systemic, graduated exercise may assist in developing and maintaining a compensatory hypertrophy.

When the compensation is no longer adequate, with symptoms and signs of a failing heart, the therapeutic indications are the same as in cardiac disease. Every effort should be made to relieve the heart of the overload and, at the same time, to support the failing myocardium.

Complete physical and mental rest should be insisted upon; relief of the right heart, by instituting **free catharsis** if the time will permit, should also be insisted upon. When the condition is critical, **venesection** should be done at once. **Digitalis**, **strophanthus**, **camphor oil**, **caffeine** and **strychnia** are some of the remedies which may be of service. Due to the degenerated myocardium, digitalis and strophanthus may have little or no effect. Strychnia is sometimes of greater service.

SURGICAL.—Adhesive pericarditis produces a fatal termination by mechanical interference with the heart and results in a cardiac dilatation. Medical treatment is helpless to prevent the formation or effect the absorption of the adhesions. Surgery has attempted to supply the demand. Weill of Lyons (1895) and Delorme (1898) have proposed that the adhesions between the visceral and parietal layers be separated, a decortication of the heart. Leriche (1909) suggested that excision of the pericardium be done and considered it preferable to the breaking down or removal of the adhesions. Neither operation has actually been done and can hardly command serious consideration because of the gravity of the surgical risk and the practical certainty that the adhesions would reform.

A safer and practical procedure, suggested by Brauer and first performed by Peterson and Simon (1902), consists in **resecting two, three or more of the costal cartilages and ribs**, with the **periosteum**, over-

lying the heart. The object to be attained is the elimination of one of the fixed unyielding points, so that the heart may function unhampered. **Cardiolysis, Brauer's operation**, is the one of choice, as it meets the indications and gives relief, providing the functional integrity of the heart is still maintained.

Prognosis.—The gravity in any individual case depends upon the extent of the adhesions and the ability of the heart to maintain a cir-



FIG. 4. ACUTE FIBRINOUS PERICARDITIS. THE PERICARDIUM HAS BEEN REFLECTED AND REVEALS THE FIBRINOUS EXUDATE AND SUBSEROUS HEMORRHAGES.

culatory equilibrium. The intrapericardial type, with partial or complete agglutination of the sac, unable to produce symptoms or signs, can have no unfavorable influence on the prognosis. Such an individual leads a normal, active life, dies, probably, from some other disease, and the pericardial adhesions are first revealed at autopsy.

With indurative mediastinopericarditis, the immediate outcome depends chiefly upon the following: the cardiac possibilities; whether the

myocardium is seriously damaged or not; the degree of mechanical hindrance; and if compensating hypertrophy has occurred. Then, too, much will depend upon the kind of life the patient can follow. The laborer, who must work at physical toil, even before he is able, who disregards his physical condition, must present a prognosis far more unfavorable than the individual with means, who can seek advice and live a life of ease and comfort. The ultimate prognosis is relatively bad, depending upon the progressive or stationary character of the lesion. Usually, sooner or later, the hypertrophy is inefficient, cardiac dilatation occurs, and the usual symptoms and signs of cardiac failure appear. Such an event is always grave and a fatal termination not far distant. Weakness and disappearance of the apex and precordial retraction are always an unfavorable sign, indicating increasing heart weakness.

Rheumatic mediastinopericarditis in early life is relatively far more serious, due to the usual accompanying endomyocarditis and the tendency to recurrence. Death usually occurs from gradual cardiac failure, with the heart in asystole; sometimes the termination is sudden and abrupt.

Morbid Anatomy.—The etiology and anatomic changes are so varied that it is possible to group the cases according to the predominating findings, which may be entirely limited to the sac, and accompanied by adjacent mediastinal and pleural pathology, by cardiac disease, or even by changes in the liver.

PERICARDIAL LESIONS.—As previously mentioned, under Acute Pericarditis, a dry plastic exudate, when limited in amount and extent, may entirely disappear and the pericardium may return to normal. Generally, perhaps with very few exceptions, the fibrinous exudate becomes organized and the pericardial layers adherent. This may be partial or complete, so that no part of the pericardial sac remains.

When partial, the adhesions may occur only at the base of the heart, perhaps posteriorly or anteriorly; sometimes they occur laterally, but rarely in the apical region. In extensive or complete involvement, the fibrous formation is always more marked on the cardiac side. When the exudate is serofibrinous or hemorrhagic, the fluid is absorbed and the same ultimate results are produced, except that simple or multiple loculation of the fluid may occur.

The purulent and tuberculous types may not only produce adhesions but go on to a cartilaginous-like or calcareous formation. The author can recall one case of an elderly man who was admitted to the hospital in a dying condition. No history could be obtained, but the clinical symptoms were those of a decompensated heart. The autopsy revealed an enormous, thickened, calcified pericardium; in fact, the heart was practically enclosed in a shell-like bag. More frequently the calcification is limited and circumscribed to certain areas.

MEDIASTINAL AND NEIGHBORING TISSUE LESIONS.—Adhesions may form and bind the pericardium to the anterior chest wall; they are usually secondary to the pericarditis. More frequently, there is an accompanying mediastinitis, which results in a fibrinous formation, fixing the obliterated pericardium to the anterior chest wall, to the spine or to the great

vessels and the esophagus behind. The same process often produces adhesions between pericardium, pleura and thoracic wall as well as the diaphragm. It is chiefly upon the occurrence of this mediastinopleurisy that the clinical manifestations and recognition of adherent pericarditis really depend. In the order of sequence, the pleuromediastinitis is usually secondary but it may be primary.

CARDIAC LESIONS.—The heart is practically always involved in pericarditis, either as a result of the same infection that produces the pericarditis or of the mechanical disturbance due to the adhesions. Simple adherent pericarditis, when the adhesions are limited to the sac in the presence of a normal endomyocardium, produces no anatomic changes in the heart. The pericardium possesses such a range of freedom that partial, or even complete, obliteration can have no injurious effect. A possible exception may occur where the adhesions are most marked about the base, and when they are particularly strong and constrict the vessels, especially the vena cava.

If the adhesive pericardium is accompanied by adhesions due to a pleuromediastinitis, or to an endomyocarditis, the heart invariably presents changes, either because of the infection or because the condition is secondary to the mechanical difficulty. Both a dilatation with hypertrophy and an atrophy of the heart have been described. Undoubtedly the former is more frequent, as the infection is prone to produce an acute endomyocarditis, while the acute pericarditis is accompanied by a limited or extensive myocarditis. Both conditions weaken the heart with a resulting dilatation, long before the sac becomes adherent. When adhesions form, the work of the heart is increased, resulting in more dilatation or in a gradual compensatory hypertrophy.

HEPATIC LESIONS.—It sometimes happens that the changes secondary to the obliterated pericardium become pronounced and dominate the clinical picture. This is particularly true in the hepatic disturbance, closely simulating a cirrhosis, which has come to be known as Pick's syndrome, or pericardial pseudocirrhosis, first described by Friedel Pick in 1896. Since then much has been written on the subject, especially by Rolleston and Kelly. Due to circulatory disturbances, the liver becomes extremely engorged with what is finally a fibrous hyperplasia. Limited perihepatitis, with peritoneal adhesions, is frequent, but this condition was considered by Pick as accidental and not an essential part of the process.

Sometimes the adherent pericardium and perihepatitis are associated with a unilateral or bilateral pleurisy and peritonitis—a multiple serositis or polyserositis. Kelly has grouped together, under the term "multiple serositis," the cases presenting the findings of a Pick's pericardial pseudocirrhosis and the "iced liver" or "Zuckergussleber" of Curschmann. Pick's syndrome is characterized by the presence of recurrent ascites, no edema of the legs, an enlarged, firm liver, and the symptoms and signs of adherent pericarditis.

Pathologic Physiology.—Adhesive pericarditis may mechanically interfere with the cardiac function by either increasing the work of the

heart or by constricting the vessels at the base of the heart. What effect the adhesions may have will be greatly determined by their location, length and density, and by the fact as to whether they are limited or extensive. Adhesions, limited to the sac, will have no appreciable effect on the heart or circulation. When the adherent pericardium is bound

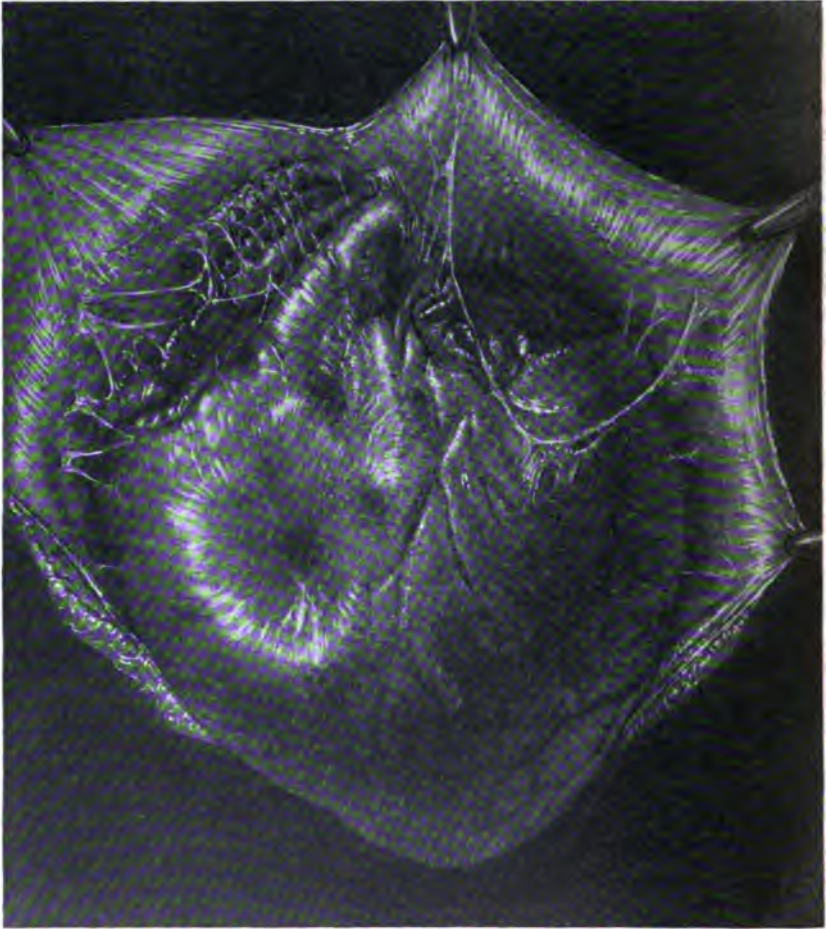


FIG. 5. ACUTE SEROFIBRINOUS PERICARDITIS. INCISED PERICARDIUM, ONLY PARTIALLY REFLECTED, DUE TO THE ADHESIONS AND BANDS OF ORGANIZED FIBRIN.

by adhesions to the chest wall, diaphragm and surrounding structures, changes in the heart and functional disturbances occur. Antedating the period of adhesion formation, the heart is usually more or less dilated, due to the myocarditis, accompanying or secondary to the pericarditis, which may be manifest by symptoms and signs. Since the period of organization of the fibrin and the formation of adhesions is relatively slow, the work of the heart is gradually increased. This results in added

physiologic activity which produces a compensating hypertrophy, providing the myocardium is not seriously damaged.

If the myocardium is in a condition unable to respond to the additional demands, no hypertrophy will occur; the heart is only more embarrassed and the circulatory disturbance more pronounced. While the adhesions, up to a certain point, may be advantageous and desirable, this is soon overbalanced by the harm and danger of cardiac dilatation, as the mechanical interference exceeds the physiologic possibilities of the heart. The traction of the firm, unyielding adhesions interferes with cardiac systole and increases the diastole, which finally results in heart failure. The clinical symptoms will be determined by the location of the adhesions, and upon which part of the heart the traction is most pronounced. If the traction is exerted on the left ventricle, the symptoms indicate pulmonary involvement, such as dyspnea, cardiac asthma, pulmonary engorgement or edema. With traction on the right heart, the disturbances are those of a systemic venous stasis, such as tricuspid insufficiency, and all the usual and familiar manifestations of a broken compensation. When the adhesions are extensive, with traction on both the right and left heart, the pulmonary and systemic disturbances will co-exist. As the adhesions become more abundant and more dense, the heart is subjected to increased traction, and dilatation is the inevitable result. The compensatory hypertrophy is no longer able to keep pace with the growing demands and heart failure occurs.

HYDROPERICARDIUM

Definition.—Hydropericardium, or hydrops pericardii, is a condition in which there is an increased amount of serous fluid in the sac; it is noninflammatory in type. It can hardly be considered as a separate pathologic or clinical entity, occurring only as a result of some other process and not as a disease. Much uncertainty exists in attempting to give a satisfactory definition, when indicating what is to be considered an abnormal amount of the pericardial fluid. Ordinarily the sac contains only just a sufficient amount to moisten the layers, but a small amount could hardly be considered as exceeding the physiologic limit. Autopsy reveals usually from 5 to 20 cc. (1.35 to 5.42 fluidrachms), or even 100 cc. (3.38 fluidounces), but this cannot be considered normal, as the pericardial fluid increases at the time of death. Hydropericardium is analogous to hydrothorax and ascites; the fluid is a transudate, clear, light straw-colored; it has a low specific gravity, an alkaline reaction, low cell and albumin content, various salts, urea and occasionally sugar. Clinically hydropericardium is a rare condition when compared with hydrothorax and ascites, although it is frequently found at autopsy.

Etiology.—Hydropericardium occurs only as a secondary process in the course of some disease, producing a disturbance of the pericardial circulation, and increasing the amount of transudate beyond the normal limit. The primary lesion may be local or general. The local diseases

include the various valvular and myocardial lesions, coronary sclerosis, thrombosis of the cardiac vessels, diseases of the lungs, as emphysema, pulmonary fibrosis and any other conditions associated with increased intracardiac pressure in the right auricle or in the coronary veins. Mediastinal tumors, aortic aneurysm and pericardial tubercle by mechanical pressure can produce the same effect.

The general causes include the diseases accompanied by a cachexia or secondary blood changes, as carcinoma, tuberculosis and nephritis. Any disease associated with a dropsy may be etiologically responsible for a hydropericardium; this means that the primary lesion may be cardiac, pulmonary, renal or general. When a transudate occurs in the various serous cavities, as in a general dropsy, the pericardium is usually involved, but the pericardial accumulation is late in its development.

Symptomatology.—Hydropericardium produces no symptoms, except when the amount of the transudate is excessive and mechanically interferes with the cardiac and pulmonary function. The symptoms present are those of the disease producing the increased transudate, whatever that may be. The fluid may accumulate slowly and reach a considerable amount without arousing any suspicion of its existence, being entirely masked by the manifestations of the disease upon which it depends. When symptoms are present, the manifestations are the same as those which occur in a pericarditis with an effusion but without the inflammatory phenomenon.

PHYSICAL SIGNS.—The findings on physical examination will depend upon the primary disease and the amount of the transudate. Generally speaking, the findings are identical with those of pericardial effusion minus the ones due to infection. Pain, fever and a friction rub are absent. In hydropericardium, the apex beat is often easily palpable and the cardiac tones good and loud, as the myocardium is less frequently involved.

Diagnosis.—The clinical recognition of hydropericardium will depend upon the physical signs of a pericardial effusion from which it must be differentiated. This may be done by a careful consideration of the history, the development of the disease, and the physical signs. Clinical manifestations of fluid in the pericardium, without a history or symptoms of an infection, associated with findings of fluid in other serous cavities, are strong evidence in favor of hydropericardium. Owing to the character of the primary disease, or to the limited amount of the fluid, and particularly as it occurs as a terminal process, the diagnosis is often overlooked. Oftentimes the diagnosis at best is but tentative and an absolute determination will depend upon a pericardial puncture. In one instance of mediastinal neoplasm with a large cardiac dullness, it was impossible to demonstrate or exclude a hydropericardium except by puncture, which revealed, on two occasions, a characteristic transudate.

Treatment.—Therapeutic efforts should be directed to relieve or minimize the primary disease. The treatment for a failing heart, pulmonary or renal disease, of which the hydropericardium is only a part, demands first attention. **Aspiration** will be necessary when the disten-

tion is pronounced and may require repeating. The relief afforded oftentimes is pronounced, but can only be temporary, as the fluid quickly reaccumulates; this, of course, depends upon the primary disease.

Prognosis.—The primary causative disease is the determining factor, not the hydropericardium, except when it reaches an unusual size and produces mechanical difficulty. Occurring usually as a terminal event, its presence indicates only a downward course and an unfavorable outcome.

HEMOPERICARDIUM

Definition.—As the term indicates, hemopericardium is an accumulation of blood in the pericardium. It is not to be confused with the hemorrhagic effusion encountered in a pericarditis or associated with a malignancy, tuberculosis or scurvy. Alcoholism and phosphorus poisoning may cause a hemorrhagic effusion into the pericardium, but it does not constitute a real hemopericardium.

Etiology.—The causes of hemopericardium may be surgical or medical. The surgical group includes injuries to the pericardium and its contents, injuries due to a stab or to gunshot wounds, and crushing injuries to the chest. Thoracic surgical operations, pulmonary or cardiac, may be a possible cause. Paracentesis of the pericardium or the heart for therapeutic purposes has been followed by a hemorrhage into the sac. The medical group includes such causes as spontaneous rupture of the heart, rupture of an aortic aneurysm or of a sclerotic coronary artery. In the order of frequency, ruptured heart stands first. When the heart ruptures, there is usually a myocardial degeneration which occurs during violent physical exertion. Less frequently the hemorrhage may be due to a cardiac aneurysm, a suppurative myocarditis with localized abscess formation, or to any condition producing a weakness of the cardiac walls, particularly when accompanied by an increase of the intracardiac pressure. When an aortic aneurysm is the cause, it is usually small and intrapericardial, but it may be located in the ascending arch, and, by dissecting downward, rupture into the pericardium. Rupture of a caseating or suppurating tuberculous tracheobronchial or mediastinal gland is a possible but rare cause, as reported by Eichorst.

Symptoms and Signs.—The symptoms are variable, depending as they do upon the amount and rapidity of the hemorrhage. If the rupture is large, with a rapid escape of blood, producing sudden distention of the sac, the symptoms of cardiac distress and heart failure will be present with a fatal termination within a few minutes or hours. The general condition of the patient may suggest that of surgical collapse. Physical signs of the hemorrhage, so far as the pericardium is concerned, are usually wanting. Most frequently the termination is so sudden that no opportunity is afforded for physical examination. When the course is less rapid, the symptoms are those of cardiac disturbance and an internal hemorrhage. The patient may experience a sensation as if something had given way in the region of the heart; perhaps anginoid pains

may be present with vertigo, syncope or convulsive seizures. Pallor, weakness, a small or imperceptible pulse may also be present. With these symptoms, the gradually distending sac presents the physical signs of an effusion, similar to those of a pericarditis with effusion or a hydropericardium. Symptoms and signs of the primary disease may also be present.

Diagnosis.—In the acute cases, the diagnosis is made usually at autopsy. The cause of sudden death may be suspected, if the patient has been under observation with some one of the diseases enumerated in the etiology. If there is a history or evidence on examination of some injury, as a stab or gunshot wound, with symptoms and signs of hemorrhage and a distended pericardial sac, a reasonable diagnosis will be possible. Obtaining blood on exploratory puncture will definitely determine the diagnosis.

Treatment.—Medical or surgical treatment in the acute cases is only a little short of useless, as it is impossible to remove or correct the cause. In the slowly developing form, the medical indications consist of **symptomatic relief** and employing such means as may increase the **coagulability of the blood**. Single or repeated **aspiration of the blood** has resulted in recovery. The surgical causes may present far better chances of controlling the hemorrhage by operation, either **ligation** or **suturing**, as the condition may demand.

Prognosis.—The prognosis is always grave; the cases due to ruptured heart or aneurysm are practically always fatal in a very short time. Penetrating and crushing injuries with a small hemorrhage may be brought to recovery.

Morbid Anatomy.—This includes the underlying primary process and the presence of blood in the pericardium. The amount of blood will depend upon the size of the rupture and the rapidity of the escape. The blood may be fluid or coagulated. When the escape is rapid, the amount is small and soon fatal. If the accumulation is slow, the sac is gradually distended; the amount of blood may be considerable and coagulated or deposited in layers, due to recurring hemorrhages.

PNEUMOPERICARDIUM

Definition.—Pneumopericardium is a collection of air or gas in the pericardium. Analogous to a similar process in the pleura, there may be a pure pneumopericardium, but usually it is combined with an effusion constituting a hydro-pneumopericardium, or with pus, a pyopneumopericardium, or with blood—a hemopericardium.

While accurately described and recognized by the older authors, it can be regarded only as a rare occurrence. W. B. James, in 1904, in a careful review of the literature, was able to find but 37 undoubted cases; with his own this made a total of 38. Cowan, Harrington and Riddell, in 1913, increased this number by 6 additional cases, 5 in the literature and their own case reported. Since that time a careful search of the lit-

erature reveals but 3 additional recorded cases, 2 of which were artificially produced for therapeutic purposes. Undoubtedly a fair number of cases occur, spontaneously or therapeutically, but are not recorded for one reason or another.

Etiology.—Air or gas may collect in the pericardium whenever there is established a communication between the sac and the external atmospheric air, or whenever gas is generated in the sac by a gas-producing organism or by putrefaction.

One group of causes includes penetrating wounds of the pericardium due to stab, gunshot wounds, and injuries of the chest, such as fracture of the ribs with injury to the lung and pleura, surgical operations and entrance of air during exploratory puncture or aspiration of the pericardium. This group constitutes a fairly large proportion, 12 of the recorded cases, 10 of which followed puncture of the pericardium.

A second group includes the causes producing a communication with an air-containing viscus, either thoracic or abdominal. Perforations of the esophagus by simple or carcinomatous ulcer or by injury with a foreign body, as in sword-swallowing, or by a fish-bone, have been reported. In 5 cases the esophagus was perforated, in 3 by carcinomatous ulceration. Among the thoracic diseases, tracheobronchial adenitis, emphysema, pneumothorax, pneumonia and gangrene have been described. In 4 cases a caseating tuberculous focus in a gland, or in the lung, established a communication between the sac and bronchus or esophagus. Air or gas may enter the sac through a communication with the abdominal organs, such as the stomach or intestines; there were 2 cases on record. Peptic ulcer, gastric or duodenal and gastric carcinoma with ulceration are the most frequent causes. Hepatic abscess as well as appendiceal abscess has been found as a possible cause.

A third group comprises those cases in which no opening into the pericardium can be found, and in which an infection of the sac exists and distention by gas from a gas-producing organism or from putrefaction. Undoubtedly some of the cases reported by the older writers were due to gas formation or to putrefaction, and very likely they were postmortem changes. Although no specific form of organism has been described, from analogy it is reasonable to conclude that the *Bacillus aerogenes capsulatus welchii* is probably one of the exciting causes, as was demonstrated in the case reported by Nicholls. *Bacillus coli* must be included as a more than likely cause. Practically any form of infection producing a purulent exudate may undergo putrefaction and gas formation.

The fourth group is composed of the cases of pericarditis in which air or gas is intentionally introduced for therapeutic purposes; this operation produces an artificial pneumopericardium such as is described by Weil and Loiseleur.

Symptoms and Physical Signs.—All symptoms may be wanting, especially when the condition develops slowly, or when the manifestations are those of pericarditis; this is particularly true of the pressure symptoms, as the sac becomes distended and interferes with the pulmonary

and cardiac function. When the air or gas enters rapidly as in perforating wounds, the patient complains of precordial discomfort, pain, dyspnea, weakness and perhaps attacks of syncope. Symptoms and signs of cardiac failure and shock may be present.

The physical findings are characteristic, in most instances permitting a clinical diagnosis as evidenced by the few cases reported by autopsy and overlooked during life. In any doubtful or questionable case, the roentgenologic examination will be definite and conclusive.

AUSCULTATION.—The most characteristic finding is by auscultation and consists of the presence of a splashing, churning sound over the precordial area; this is due to the presence of fluid and air, or gas, in the pericardium. These sounds are extremely variable in time and quality but quite synchronous with the heart's action. A metallic tinkling is often heard, superadded to the splashing sound, sometimes heard by the patient and audible for some distance from the patient. The splashing sound has been described by various writers as the "mill-wheel" murmur, the bruit de moulin, and a metallic gurgling. As the fluid increases, the characteristic sounds decrease and may disappear, and the cardiac sounds become distant and muffled.

PERCUSSION.—On percussion, with the patient recumbent in the dorsal position, tympany is present over the cardiac area; with the patient sitting upright, there is tympany over the upper and dullness over the lower portion of the pericardium. Change of position may produce a change in the percussion findings. Occasionally dullness over the air- or gas-filled sac is found instead of tympany, due to the degree of tension present. Cracked-pot sound has also been described, where only a hydro-pneumopericardium was found without a bronchial communication. The cardiac impulse may be palpable only in the recumbent position; absent or doubtful in the upright. Findings of the associated cardiac and pericardial pathology, as well as the primary disease, may also be determined.

ROENTGENOLOGIC EXAMINATION.—Confirmatory and conclusive evidence is furnished by roentgenologic examination. Usually this examination leaves no room for doubt in the presence of the characteristic physical signs, but, if it is not a part of the regular routine examination and any doubt does exist, the patient should be subjected to such an examination.

The fluoroscopic findings and skiagrams are both most characteristic, showing the presence of air or gas in the distended sac. A fluid level, shifting with the position of the patient or with cardiac action, can easily be demonstrated when the pneumopericardium is associated with effusion or exudate into the sac.

Diagnosis.—With the typical physical signs and particularly with a roentgenologic examination, the diagnosis is easy. There is hardly any other condition which simulates pneumopericardium or produces any confusion. It is conceivable that a pulmonary cavity situated near the heart or perhaps a left-sided pneumothorax might cause some difficulty. Suspension of the abnormal metallic sounds with suspension of breathing,

the displacement of the heart to the right, along with palpable cardiac impulse and audible heart sounds, will assist in diagnosis. Roentgenologic examination will remove all doubts and determine the diagnosis. Traumatic emphysema with air in the pericardial area may be confusing and cause a slight suggestion of pneumopericardium. The stomach distended by gas sometimes is associated with a metallic sound, but differentiation is made possible by careful cardiac examination or by aspiration of the stomach contents.

Treatment.—This must depend chiefly upon the cause as well as the form of the pneumopericardium. If produced by a penetrating external wound, the opening should be closed and treated surgically. In the event of a pericarditis developing, the same measures are indicated as outlined in the treatment of that disease. When it is due to an internal penetrating wound or fistulous tract, the treatment is purely symptomatic and palliative.

Accidental and unintentional entrance of air into the pericardium during puncture or aspiration should cause little anxiety, as the air is usually rapidly absorbed. Therapeutically it may be of assistance in the treatment of the disease for which the puncture or aspiration was made.

Prognosis.—Pneumopericardium, with its varied etiology, presents a prognosis based mainly upon the primary disease, many of which cases are fatal. When due to the accidental entrance of air during puncture or aspiration of the pericardium, the prognosis is usually favorable, depending upon the type of pericardial involvement.

Morbid Anatomy.—The anatomic changes consist of air or gas in the pericardium with the associated pathology. Pure pneumopericardium is extremely rare; most frequently a pericarditis is present with a serous or purulent, and occasionally hemorrhagic, exudate.

The air or gas occupies the upper portion of the sac, with the fluid in the dependent part. The composition of the air or gas will vary according to the etiology. It may be identical with atmospheric air when the communication is external or similar to that found in the lungs, stomach or intestines, depending upon the location of the perforation. In the closed cases, the gas is usually fetid and foul-smelling. Puncture of the pericardium will allow the air or gas to escape with, sometimes, a distinct sound.

NEOPLASMS OF THE PERICARDIUM

The pericardium may become involved with a malignant or benign neoplasm, which may be primary or secondary.

Malignant Neoplasms.—Either carcinoma or sarcoma may occur. Primary involvement with either form of malignancy is extremely rare. Primary carcinoma is even denied or seriously questioned, but as a possibility it must be admitted. Foster and Guarnieri have reported primary pericardial carcinoma. Broadbent, Redtenbacher, and Williams and Miller have reported primary sarcomas.

Secondary malignancy, while more frequent, is also relatively rare, occurring but six times in 9118 autopsies according to Kobler. Either carcinoma or sarcoma may occur, but the former is more frequent. Usually the primary growth is located in the chest and involves the pericardium by direct extension or by metastases. Mediastinal, bronchial, esophageal, gastric, pulmonary or pleural malignancy is responsible for the greater number. Malignancy of distant organs, with metastatic secondary growths, may also occur. The secondary neoplasms present

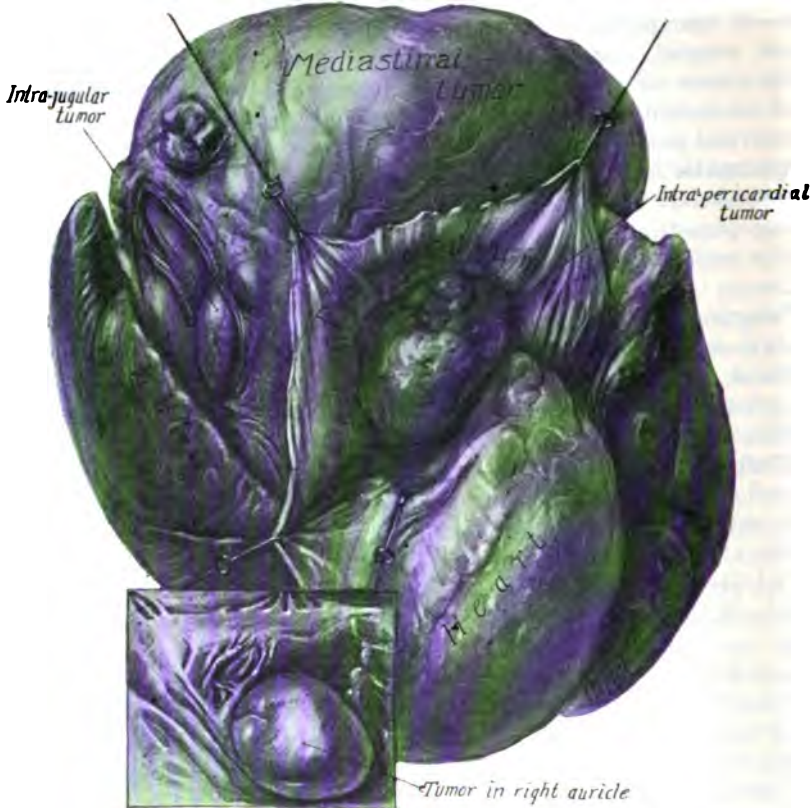


FIG. 6. ANTERIOR VIEW OF LYMPHOSARCOMA, WITH LARGE MEDIASTINAL NEOPLASM, ALSO SHOWING GROWTH INTO PERICARDIUM, RIGHT AURICLE AND RIGHT JUGULAR VEIN. (Courtesy W. B. Saunders Co.)

the same appearance as that characteristic of the primary growth. The secondary pericardial growths may be single or multiple, with or without an associated hydropericardium or pericarditis. Located at the base of the heart and with pressure on the coronary circulation, a pericardial transudate can occur. Usually there is more or less pericarditis with a hemorrhagic exudate. Occasionally a purulent or putrid exudate is present, probably due to secondary infection.

SYMPTOMS AND PHYSICAL SIGNS.—The symptoms are those of the primary growths associated with the acute or subacute manifestations of a pericarditis. Physical findings will vary according to the anatomic changes; in some the findings will be entirely negative, while in others they will be those of a pericarditis with effusion or of a hydropericardium. Evidence of a primary growth, as a mediastinal tumor, regional adenopathy or enlargement of the cervical glands, will be of considerable assistance in the diagnosis.

Roentgenologic examination is indispensable and should always be employed. When the findings indicate fluid in the sac, exploratory puncture or aspiration, when indicated, will furnish valuable diagnostic information. Usually the fluid will be found to be bloody, but it may be clear, purulent or putrid.

Diagnosis.—The recognition of pericardial malignancy depends upon the determination of a primary malignancy, associated with pericardial symptoms or signs of a pericarditis. Without these conditions the diagnosis may be impossible.

Treatment.—The treatment is purely **palliative** and consists in rendering relative comfort. **Opiates** are frequently required to relieve pain or to produce rest. **Repeated aspiration of the sac** may be necessary, or, perhaps, the establishment of **permanent drainage**.

Prognosis.—The prognosis is necessarily bad and the duration usually brief, as the pericardial complication is indicative of extensive involvement.

BENIGN NEOPLASMS.—Nonmalignant neoplasms have been reported, chiefly as autopsy findings. Clinically they present little or no interest as their recognition is practically impossible. The reports include fibroid tumors, lymphomas, one case of cystic enchondroma, polypi and cardioliths. Free bodies in the pericardium, probably from detached polypi, a mass of fibrin or coagulated blood, have also been described.

History.—Pericardial lesions were first recognized and described by Galen from the anatomic investigations and dissections in the lower animals. Senac, by his dissections in man, advanced the knowledge on pericardial diseases but only from the anatomic standpoint. The same may be said of Vienneseus, who first described pericardial adhesions, and Griesinger, in his description of mediastinopericarditis. Morgagni made the first attempt to correlate his pathologic findings with the clinical symptoms. With the discovery of immediate percussion, Auenbrugger applied his method to the clinical recognition of pericardial disease, which was finally enthusiastically adopted and employed by Corvisart. To Laennec is due the honor of first detecting the pericardial friction rub by auscultation, which he believed at first was due to a pericarditis, but later, unfortunately, this view was discarded. Equal or greater honor is due Collin for first accurately and positively associating the rub with a pericarditis. Among the long list of clinical investigators, the name of Skoda stands preëminent, due to his acute and accurate interpretation of the physical signs of pericarditis.

With the possibility of the recognition of pericarditis, attention was directed to its association with other diseases, especially rheumatism as emphasized by Pitcairn, Dundas, Sibson, Wells and Latham. Bacteriology, by demonstrating the essential causative factors, has furnished an important chapter in the knowledge of this disease.

Riolan proposed tapping the pericardium, but Romero was the first actually to perform pericardicentesis. Schuh and Skoda placed pericardial puncture and aspiration on a safe clinical basis. The latest noteworthy addition to our knowledge in pericardial diseases is due to the application of the roentgen rays.

There is an intentional break in the continuity of page numbers between these chapters. The space will be utilized by future revisions of the text in this volume.

CHAPTER V.

ANGINA PECTORIS

By ALEXANDER LAMBERT, M.D.

Definition, p. 253; Etiology, p. 253; Symptomatology, p. 259; Diagnosis, p. 265; Complications and sequelæ, p. 267; Association with other diseases, p. 267; Clinical varieties, p. 267:—Angina sine dolore, p. 268; Pseudo-angina, p. 269; Toxic anginas, p. 269; Abdominal angina, p. 271;—Treatment, p. 272; Prognosis, p. 276; Pathology, p. 277; Historical summary, p. 278.

Definition.—Angina pectoris is not a disease in itself but is best defined as a symptom complex characterized by pain in the chest which may be of the uttermost intensity, rarely failing to convey with it the fear or the conviction of impending death. Angina pectoris kills through the vagal inhibitory mechanism in the heart. The original morbid process which sets in motion the fatal cardiac inhibition is of varied origin.

Etiology.—Medical opinion regarding the causation of angina pectoris has varied during the last century and a quarter, since Heberden first called attention to this group of symptoms, according to the changes in fashion of medical theories. At first it was produced by spasm rather than inflammation. Later, it was a question of arterial pressures and tension. At one period, the discussion hinged around the differences in the coronary blood supply and the spasm or intermittent claudication of these arteries. At another period some unknown conditions of exhaustion or disease of the myocardium have sufficed to explain the symptom complex. Running through it all was the urgent necessity in the medical mind of finding the definite pathologic lesion to explain the group of symptoms which could so suddenly appear without previous warning in a man in vigorous health, and in many instances be so quickly fatal. That disordered function or a perversion of a normal function could kill without concrete pathologic lesion did not seem possible. Huchard has collected the various ideas of many physicians from different periods and gives some sixty-four different opinions to explain the causation of angina pectoris. Since Edward Jenner, the friend of Heberden, found that in most patients dying of angina, the coronary arteries were diseased, coronary disease has usually been considered as the underlying cause of the pain and cessation of cardiac action. This has been generally accepted in spite of the fact that postmortem examination showed that the majority of patients with diseased or calcareous coronaries had not suffered during life any symptoms of angina pectoris and in

many patients who had died of angina, the myocardium was practically normal and the coronaries healthy. The Viennese school of Bamberger and Von Neusser has for many years insisted that the symptom complex had as its foundation some morbid process which set in motion the sensorimotor arc of the vegetative nervous system involving the mechanism of the heart's action.

The separation of diseases of the heart from diseases of the blood-vessels in medical teaching and thought, has also retarded an appreciation of the correct interpretation of the anginal complex. In the minds of most observers, both laymen and physicians, the intense precordial or substernal pain often accompanied by cessation of the heart's action could only be conceived as due to a disease of the heart itself. Among the valuable contributions which Mackenzie has made in the study of the heart and circulation, is the conception of the sensorimotor reflex as a means through which the viscera express in terms of pain, certain disturbances of function or morbid changes in their tissues. We do not to-day know what pain is in the final analysis but we do know that both the vegetative nervous system, and the cerebrospinal system of nerves possess fibers which, going through the posterior root of the spinal nerve, produce a sensation in consciousness, which we call pain. In the vegetative nervous system, this reaction in the sensory fibers causes a return outflow of nerve action in either or both neural systems which results in definite motor responses, producing increased or diminished function in somatic muscles or viscera, or often cessation of all function. Whether we accept the myogenic or neurogenic action as the origin of cardiac function is of no consequence, since in either case, the sympathetic portion of the vegetative nervous system possesses motor power to increase enormously the cardiac action or, the autonomic portion through the vagus can slow down its mechanism or inhibit all action. It is only through some such general conception as this that one can explain the varied pathologic findings in those patients who have died showing the symptom complex of angina. The most common lesion found post-mortem is that of an aortitis in the first portion of the ascending aorta. In about one-third of the cases the coronary arteries are definitely stated to have been healthy and not diseased. In most cases the myocardium has shown various forms of myocardial disease or degeneration. In many instances, however, this too has been reported healthy and not diseased. Morison reports attacks of angina occurring in a patient who showed on postmortem examination an intravascular aneurysm of the right coronary artery. Pericarditis is also another causal factor in producing angina pectoris, especially pericarditis which occurs around the base of the heart involving the insertions of the great vessels, especially the aorta. Sir Clifford Allbutt reports a case in which no lesion was found except inflammatory adhesions around the root of the aorta from a previous attack of pericarditis. Von Neusser reports the case of a patient who, two years after rheumatism, showed typical signs of angina pectoris and the postmortem examination showed only adhesions

of the heart to the pericardium, while the coronaries and the aorta were absolutely normal at their origins. Von Neusser also reports a case of angina pectoris in which there was a tumor on the left vagus and on the right phrenic nerve, with a similar tumor growing on the large cardiac nerve, and the heart, except for being "flabby," showed no lesions. Death has occurred in a paroxysm of angina pectoris as reported by several observers, both in young patients with normal hearts and in old patients with diseased hearts, during the passage of gall-stones. It is not an uncommon occurrence for an obliterating thrombosis of the various arteries of the coronary system to occur, bringing on the most terrific attacks of anginal pain, in which death not infrequently occurs. Other patients, it is true, have thrombosis of the coronary arteries without pain and die therefrom. Still others go on living in spite of coronary thrombosis. Verdon claims that the exciting cause of the symptom complex of angina pectoris is due to spasm of the gastro-esophageal portion of the alimentary tract or to some undue traction on the esophagus as from an over-distended stomach. This author believes that the symptom complex is an expression of a segmentary neurosis in the cord, the inflammation of each neuron or the neuronitis, as he expresses it, being proven by the persistent areas of peripheral pain and tenderness in the skin in various areas on the chest wall, so noticeable in many patients who suffer the attacks of lesser intensity of angina, or even in those who suffer from severer attacks. Other cases are reported where inflammation around the celiac axis and the abdominal aorta had given rise to attacks of anginal pain. Vasquez and Balfour have both expressed the belief that the pathological dilatation of the cardiac muscle produces, in some instances, attacks of angina. The pain occurs as the left ventricle dilates, but this is not a universal observation, for it has been a noticeable feature in certain patients suffering from attacks of anginal pain, that when their heart had dilated the attacks of pain ceased, and Musser among others, has reported a patient in whom the attacks of pain ceased when the heart had dilated, but reappeared when the cardiac muscle had sufficiently recovered to overcome its dilatation. It is evident therefore that the symptom complex of angina pectoris accompanies many morbid conditions which have as a pathologic basis equally varied lesions. The one common factor in all the different lesions is the possible involvement of the sensory fibers of the vegetative nervous system, thus setting in motion the sensorimotor reflex producing the symptom complex of angina pectoris.

The clinical outbreak of angina pectoris occurs most frequently in men at the time of life when senescence has begun but before senility is established. It occurs, therefore, most frequently when arteriosclerosis has begun and the health of middle age has begun to wane. When once old age is established with calcification of the coronary arteries, the symptom complex of angina does not so frequently occur. Angina shows itself as a symptom complex of rheumatic aortitis even in childhood or in youth or it follows an attack of influenza from an

aortitis which may occur in youth, in middle life or old age. It very frequently follows the infection of syphilis when that disease attacks the aorta, producing an aortitis or an aneurysm. It follows, therefore, those forms of aortitis in which the vasa vasorum are the channels through which the inflammation proceeds in the adventitia and through it to the media producing a mesarteritis, in which the intima is only secondarily involved. When once the morbid basis which starts the anginal reflex is established in aorta or heart, the attacks may be produced by any undue exertion or even by the slightest exertion which upsets the existing equilibrium in which pain is not present. A sudden increase of blood-pressure produced by exercise, particularly a slightly increased rapidity of walking after a meal or walking against the wind or up a distinct grade or ascending stairs, are all sufficient to start the reflex into activity. It may follow any exciting emotions or it may follow the acts of defecation or of coitus. A person who is in such unstable equilibrium is in danger from any excessive emotion and especially from anger or excessive joy. The pain of angina pectoris follows also the intoxications of tobacco, lead, gout or diabetes. Whether in these instances it is due to true intoxication as from tobacco or whether it is produced by arteriosclerosis which accompanies these other conditions cannot be said with certainty. Tobacco, according to Huchard, produces lesions in the aorta and also attacks of angina without visible tissue changes. Most clinical observers agree, however, that when once aortitis is present, tobacco increases both the frequency of the occurrence and the severity of the anginal complex. Valvular diseases of the heart are not as a rule accompanied by the anginal complex of symptoms. Lesions of the aortic valve which are naturally extensions of the disease processes in the aorta, are the lesions with which angina is most often evident. Mitral stenosis, however, is sometimes accompanied by attacks of true anginal pain and these occur in patients in whom post-mortem examination shows healthy coronary arteries. Beginning aneurysms of the aorta are also at times accompanied by anginal pain due in all probability to the same reflex mechanism which produces angina in the mesarteritis without the aneurysmal sacculation or dilatation.

Sir Clifford Allbutt is correct in his contention that the most frequent underlying morbid process of angina pectoris is an aortitis in the subsigmoïdian area of the aorta. He does not, however, seem satisfied to accept the fact that Manouelian and others have demonstrated sensory endings of the nerve fibrils in the aorta, adventitia and media, but believes that there must be present pacinian nerve-endings of sensory nerves to account for the sensory reflex being set in motion. These pacinian nerve-endings have not yet been proven to exist in the aorta but they have been found in other blood-vessels. Physiologists are beginning to ascribe sensory functions in nerve-endings in the abundant nerve supply to the sinuses of Valsalva at the commencement of the aorta and around the auricular ventricular orifices. Recent investigators also show nerve fibers and ganglia scattered through the heart, and some investigators claim to have found sensory nerve-endings in the heart

itself. The enervation of the heart and the aorta and the sensory paths from these regions are not finally worked out but the evidence seems sufficient to justify the belief of the existence of a sensorimotor reflex produced by the nerves running from and to the heart in the sympathetic and the vagus systems. There is no question but that the distribution of pain in the anginal attacks can be explained by the anatomical distribution of known nerve fibers. The idea that angina pectoris is of nervous origin and not of muscular or vascular causation is not new. It has been held in France by Bouillaud and Desportes; by Rombert in Germany; by Bamberg and Von Neusser in Vienna. Sir Clifford Allbutt, who most energetically denies either vascular or muscular origin and who has put aside all theories of nervous origin, falls back in his final analysis on an aortitis or an inflammatory process giving rise to an involvement of sensory nerve-endings and acknowledges that only through sensory nerve-endings is the painful reflex set in motion. His explanation, therefore, is one of nervous etiology of angina pectoris, especially since in some instances of aortitis produced by the same inflammatory processes anginal attacks do not occur. Vasquez divides the etiology of angina pectoris under two heads: (1) That of angina produced by effort, and (2) the angina of repose. The former follows exertion and is due to lesions in the aorta, especially in the subsigmoidal area. The latter occurs during sleep and in Vasquez' opinion, the painful reaction follows a distention of the left ventricle and secondarily of the aorta, the idea being that the left ventricle as well as the aorta, surprised suddenly by hypertension is distended excessively and the excitation of the nerve filaments of the myocardium, in consequence, is transmitted to the cardiac plexus producing the symptoms of angina pectoris. The theory often accepted that the pain is produced by spasm or by anemia of the cardiac muscle seems highly improbable especially since, in many cases of even severe attacks of angina, the pulse does not vary in frequency, force or tension until just before death. In angina due to coronary thrombosis, the pulse is often very rapid and may be irregular or small and feeble, but coronary thrombosis is not the usual lesion underlying the anginal attack. If there were a spasm of the muscle, or if there were deviation from normal in its contracting power, it would seem most probable that there would be evidences of it in the pulse. Moreover, the cardiac muscle does not go into tetanic spasm in the manner of a skeletal muscle. Irregularity of the conducting mechanism would show in irregularity in the pulse and while this sometimes occurs, the contracting system of the myocardium is the only mass which would influence the force of the pulse. Moreover, if the heart contracts, it does so with all its vigor under Bowditch's law. The same is true of intermittent claudication of the coronary arteries causing anemia of the myocardium. All cardiac pain is not of a single origin and the morbid processes which produce myocardial exhaustion or disease do not account for the intensity or kind of pain evident in anginal attacks. These processes in the myocardium produce dyspnea and breathlessness but do not produce the anginal pains. The absence of dyspnea is a

striking fact in the symptom complex of angina pectoris. Von Neusser draws attention to the fact that in intermittent claudication of the peripheral arteries there must be a spasm of the muscles of the media as well as stenosis of the lumen and whether it is through the hypertrophied layer of the muscular coat or through the irritation of nerve-endings, the pain produced is caused as much by this as by the anemia brought about by the stenosed lumen of the vessels. Pain is caused in intestinal spasm by the irregular contraction of the muscular layer of the gut, as in colic or pylorospasm, and it may be that in the aorta with a diseased media there may be areas of irregular contraction, even if not of spasmodic tension which in some instances produce the pain. Mackenzie reports a case in which the arterial pressure was 190 during the attack. Nitrites relieved the attack and some minutes after, when the patient was comfortable and free from pain, the pressure had risen to 200. It was, therefore, not the pressure but some added element which produced the attack of angina. Nitrites relieve the spasm by inhibiting the vasoconstrictor nerves. It is, therefore, not improbable that in many instances we are dealing with some tension in the muscular layer, involving the sensory nerve-ending, of the aorta which brings about this intense pain.

There is no question but that diseased coronary arteries and the diminution in the lumen of the coronaries is in all probability a very great factor in the immediate causation of death, but death in one-third of the cases that have come to postmortem has occurred with healthy coronaries and in many instances with healthy cardiac muscles.

That the sensorimotor reflex may start equally from the aorta or the heart, the clinical evidence is conclusive. Both the heart and the aorta are amply supplied with nerves from the sympathetic and vagus systems. Besides the sympathetic vasomotor nerves the aorta is supplied by both vagus and sympathetic nerves from both the superficial and deep cardiac plexuses, particularly around the aortic root at the junction with the heart. The right and left coronary plexuses not only surround the opening of each coronary artery but spread around on the adjacent areas of the aorta as well, and both these plexuses receive fibers from both the superficial and deep cardiac plexuses. The depressor nerve in animals, such as the rabbit, described by Ludwig and Cyon is an afferent nerve. Its homologue in man is described by Tandler as descending separately or in the sheath with the superior cardiac sympathetic nerve and is made up from the upper heart branches of the vagus and by a branch from the external branch of the superior laryngeal nerve of the vagus. It spreads out and terminates upon the aorta, not going to the heart itself. Its function seems to be to carry to the sympathetic ganglia those stimuli necessary to regulate the vasomotor control and the rise and fall of blood-pressure through reflex stimulation of the splanchnic area and abdominal vessels.

It is believed that the vagus contains constrictor nerves going to the coronary arteries. An accurate description of the entire afferent tracts of the sympathetic nerves cannot be given. It is at present unknown.

The sensory motor reflex arc, however, is present and one expression of its efferent action is seen in the vagal inhibition of the heart. The condition of the coronary vessels, probably, or of the myocardium may turn the scales for life or death. Hearts which possess healthy muscular systems and undegenerate coronary vessels resist best the vagal inhibition and a healthy heart will often overcome the attack even though it be serious, but a heart crippled in its blood supply or in its myocardium, has lost its power to overcome the fatal inhibition. The conducting system of the heart possesses a vascular supply separate from the general muscular mass of the heart but we must look to the future to show the differential diagnosis indicating when this branch of the right coronary artery is cut off from its blood supply. Even, however, in hearts not crippled by disease and possessing the resiliency of youthful tissue the recuperation of healthy cardiac muscle with normal vessels may fail to occur, and the reflex inhibition may cause a permanent cessation of all cardiac action.

Symptomatology.—The chief and most characteristic symptom of angina pectoris is pain. This is usually a substernal pain at the right or left of the sternum about the level of the third rib, or it may be under the manubrium or it may be under the xiphoid. The pain begins as either sharp and stabbing or tearing, or as a dull grinding pain that carries with it the feeling as if the chest were being held and then crushed in. The pain usually radiates upward to the shoulder or back under the left scapula, and if going to the shoulder, it continues on down the arm to the elbow or, following the ulna nerve, ends in tingling pain in the fourth and little fingers. At times the pain is only localized in the wrist or may appear as a burning ache on the inside of the upper arm or it sometimes remains in the arm and is not felt in the chest. Sometimes, it begins in the arm and goes upward and on to the chest. Usually, however, it starts in the chest and goes down the left arm. In the majority of cases it radiates to the left but it may, however, radiate to the right arm or simultaneously to both arms. In dextrocardia, the pain is still on the left side. The pain may not go towards the arm. In some individuals it begins in the third space or in the center of the chest, goes up along the vessels of the neck and ends as an intense gripping pain in the constrictor muscles of the pharynx or in the notch between the mastoid process and the jaw, driving the pain into the ears or on the side of the neck, or it radiates into the face or jaw itself along the second and third branches of the fifth nerve. It may shoot out from the chest to the left shoulder and the top of the trapezius. In three persons in the experience of the author, the pain has been most severe in the third left intercostal space and in the insertion of the accessory nerve on the left in the trapezius and also in the great occipital nerve in the back of the head. In other patients the pain radiates down the leg. Osler and Huchard report cases where the pain radiated down into the testicle and was followed by swelling of the testicle. Sometimes the pain begins in the back and then passing to the front, follows the usual course of left radiation in the arm. A division is sometimes made of a

special kind of angina pectoris in which the pain begins in the epigastrium and is designated as abdominal angina.

To understand the symptoms of pain and its distribution and varying radiation in angina pectoris, one must remember clearly the anatomical description of the sympathetic and vagus nervous systems. The vagus nerve as it issues through the jugular foramen, sends off from the jugular ganglion an auricular branch going to the drum, to the external auditory meatus and to the auricle of the ear. It is through this nerve that anginal pain is carried to the ear. This nerve is considered to be associated with the trigeminus and accounts for the pain in some instances occurring in angina, in the jaw itself and in the teeth. The tenth nerve or vagus proper is a sensory nerve to the pharynx, esophagus and stomach and respiratory organs. This is joined at its ganglion nodosum by the accessory or eleventh nerve, which carries the motor nerves to the vagus and then goes to the palate and the pharynx and the respiratory organs, and carries the inhibitory fibers of the heart. It is through the pharyngeal branches that the gripping spasm in the throat is so intensely felt in anginal attacks. It is also the motor nerve for the alimentary canal. It is the motor nerve to the upper portion of the trapezius and the sternomastoid muscles. These last two muscles embryologically are derived in part from the branchial arches and formerly belonged to the respiratory group. Tenderness and hyperalgesia are very commonly present at the insertion of the branches supplying these muscles following an attack of angina. From the ganglion of the root of the vagus, a nerve goes over and joins the connecting branch of the second and third cervical nerves. It is probable that through this nerve pain extends back of the ear over the neck and scalp in either the great auricular nerve to the side of the neck, or on to the upper portion of the ear itself by the little occipital nerve, or along the back of the head through the great occipital nerve, extending by this nerve over the scalp to the crown of the head. Radiation in this area cannot be infrequent, as in the author's experience it has been very definitely evident in three patients. The gripping spasm of pain in the throat in some attacks of angina pectoris, which have come under the author's observation, occurs most frequently in those cases of angina which occur with diseases of the aorta.

As the vagus descends into the neck it sends off branches from the main trunk to the heart and also cardiac branches from the superior and inferior laryngeal nerves. These branches pass to the cardiac plexuses, the upper cardiac branches of the left vagus and fibers from the left lower cardiac nerve forming the superficial plexus with the left superior sympathetic nerve. The deep cardiac plexus is formed by all the other nerves coming from the vagus and the sympathetic. These two plexuses anastomose with the esophageal, bronchial, and anterior and posterior pulmonary plexuses and are the pathways through which the inhibitory action on the heart occurs in operations of the pleura and lungs. The sympathetic nerves come down into the neck from the superior ganglion from the middle sympathetic ganglion when present, and from the in-

ferior ganglion when this forms a separate ganglion or joins with the first thoracic ganglion to form the stellate ganglion. The sympathetic nerves coming from the upper five thoracic nerves go up and join the sympathetic cord in the neck. The lower thoracic sympathetic nerves, although distributed chiefly in the abdomen, send some of their fibers directly to supply the lungs, aorta and esophagus. The accelerator fibers of the heart are efferent sympathetic fibers emerging from the spinal roots of the second, third and fourth thoracic spinal nerves. It is also said that some of these fibers may be found in the first and fifth thoracic and often in the lower cervical nerves. They pass then, by way of the white rami to the first thoracic ganglion and thence to the lower cervical ganglion and are given off from the loop of Vieussens, going from there to the cardiac plexus. No accelerator fibers are found above the inferior cervical ganglion. The cardiac inhibitory center is that of the nucleus ambiguus from which rise the motor fibers for the vagus and the glossopharyngeal nerves. The vagus also carries afferent fibers through the abdominal viscera and the heart may be reflexly inhibited most readily by the stimulation of the surface of the abdominal viscera or by a blow thereon or by sudden distention of the stomach. The radiation in the cervical nerves is to the second and third segments as just mentioned. Then, skipping the fourth, fifth, sixth and seventh segments, the pain follows the inner aspect of the arm in the segments of the eighth cervical and in the first and second thoracic. On the chest wall from the first to the eighth thoracic segments, especially the regions supplied by the third and fourth thoracic, are the areas showing sensitiveness and pain from the cardiac reflexes. The pain is therefore distributed in the areas supplied by the intercostobrachial, the medial cutaneous of the arm and of the forearm and the ulna nerves. Radiation downward probably must go from the aortic plexus through those nerves coming up from the lower thoracic fibers. A branch from the twelfth thoracic nerve enters frequently into the formation of the lumbar plexus and the genitofemoral nerve is formed by a branch of the first and second nerves of this plexus. From this genitofemoral nerve a small external spermatic branch is given off. It is probably through the branch to the spermatic plexus of this nerve that the unusual distribution of the anginal reflex has been observed to extend to the testicle. The internal sphincter of the rectum is supplied by both thoracic fibers of the sympathetic system coming down through the inferior mesenteric ganglia and sacral fibers of the vagal system coming to it through the second, third and fourth sacral nerves. The inferior hemorrhoidal branch of the pudendal nerve also sends fibers to the sphincter. The sensorimotor reflex has pathways here for its conduction through thoracic connections. But probably straining in the act of defecation more often produces anginal attacks similar to these produced by exertion, especially in patients in whom the paroxysms start from slight exertions. The attacks of angina occurring so frequently in elderly men during coitus may arise through reflexes produced in the vegetative nerve fibers in the branches of the pudendal nerve to the external genitals. But most

probably emotional excitement and physical exertion play a large part in originating these anginal attacks.

The patient seized with an attack of angina pectoris stops where he is. He is usually found sitting or standing perfectly still with his hands and arms pressed to his sides rigidly holding himself, fearing even to breathe lest he increase the pain. Often he is found with his hand grasping his upper arm or wrist or pressing against his chest where the most intense pain seems to be centered. He may cry out with the intensity of the pain, and a few roll about in agony. The face becomes pale and looks pinched and drawn and the perspiration starts from the forehead and runs down the face. In some there is an abundant flow of saliva into the mouth which even may overflow and run out of the sides of the mouth and over the chin. With this intense pain there comes the fear of approaching death, or, in many patients as expressed by them, it is more a certainty of approaching dissolution than the fear of it, for it does not seem to them that they can suffer more and still live. Or, the feeling may be one of intense apprehension or anxiety. In some patients there is a feeling of globus with the sensation that could they but rid themselves of a mass of gas from their throat or stomach they would be relieved and in many patients there frequently is an eructation of gas or vomiting or large amounts of flatus are passed from the bowel. In some attacks the pain during the attack lasts but a few minutes and subsides as suddenly as it arises. In other instances, the attack may subside but may recur on very little exertion on the part of the patient and this condition may continue for many hours. In the mild attacks the pain does not reach its full intensity, for the patient appreciates the warning and stops whatever he is doing. Usually the pain in the chest subsides first, then the arm pain ceases, but numbness disappears more slowly. Those patients in whom angina is brought about by exertion can stop walking, if that be the cause, and wait until the pain ceases and then go on, and gradually, the heart becoming accustomed to its increased work, can perform it without giving the distress. After an attack of anginal pain, there is often left an area on the chest wall of hyperalgesia. This is particularly common over the pectoral muscle and along the anterior axillary line, sometimes extending upon the inner side of the arm. It is also not uncommon to find a tender spot over the third rib on either side and in the sternomastoid or trapezius muscles where the accessory nerve enters. Verdon describes cases of angina in nervous high-strung women who were having frequent attacks and in whom the variation of the areas of tenderness as they appeared in the intercostal spaces occupied different areas from time to time in front and behind on the chest wall. These patients often showed points of tenderness over the dorsal processes of the vertebrae. The intensity of the pain is not always in proportion to the gravity of the attack. Mild nagging attacks may be the forerunners of the severest forms, or severe attacks may subside and cease to recur. In the very gravest forms of angina there may be almost absence of pain and patients dying quickly often do not seem to suffer the full intensity of

agony. There is a form of angina without pain usually designated as *angina sine dolore*, in which the patient shows the cardiac weakness and collapse and the anguish with the fear of death but with no pain.

In many cases the pulse remains normal and the heart does not quicken its rhythm. Often in the most intense attacks the heart beats quietly in its normal rhythm until the vagal inhibition starts, often suddenly. In other attacks the pulse becomes full though regular and may beat as low as 28 or 30 to the minute. In these cases the heart feels to the patient as if it were bursting or had stopped suddenly and was still. The pulse may be rapid and feeble or small and tense, especially in those cases where there is coronary thrombosis. In some cases it may be slightly increased in frequency. It is sometimes reported as being small, soft and compressible or small and tense. In other cases, extra systoles have been known to occur. In some patients with cardiac insufficiency and arrhythmia between the attacks, the pulse becomes regular during the paroxysms and cardiac murmurs have also been noted to disappear during the paroxysm. In some patients there has been noted a surprising smallness of the left radial pulse as compared with the right. This peculiarity may exist in patients without the existence of aneurysm. The respiration is usually but little affected. It is characteristic of the pure uncomplicated cases of angina pectoris that there is no sign of dyspnea but on the contrary, apnea is present. Patients at times will take a long breath and hold it in order to inhibit any possible movement of the chest that might in any way increase their pain. The usually normal pulse and lack of dyspnea distinguishes true anginal attacks from both cardiac asthma and the dyspneic attacks of chronic cardiac diseases. After the angina attacks have extended for some length of time, cardiac dyspnea may come on. In the coronary thrombotic cases of angina there may be a definite sense of shortness of breath and some evidence of dyspnea. In these protracted cases of angina pectoris, cyanosis and pulmonary edema with bloody expectoration may occur. In some patients it is reported that they suffer from alternating attacks of dyspnea and true angina. Between attacks of angina, Cheyne-Stokes breathing is met with, particularly between very severe attacks.

The symptom complex of angina is characterized as much by the horror of immediate death as by the intensity of the pain. In the extreme degree, the conviction of impending dissolution is said to be almost peculiar to angina pectoris. Often in the first attack, even when this is not of great intensity, there is a peculiar creepy horror in consciousness that the number of one's days is fulfilled. It has been variously described as a conviction that death is imminent, rather than a fear of dying. Death seems inevitable and inescapable and one therefore waits in benumbed agony for it to come and blot out the suffering. The severity of the pain and the intensity of the horror do not run parallel. Often with slight or minor attacks of angina the horror is the striking feature of the paroxysm or the reverse may be true; there may be intense pain and yet no fear of death. Allbutt says that in his experience, in young persons the horror is less manifest and often absent. It seems

in older persons, that this shadow may even obscure the pain and that many of these sufferers dread more this death portent than even the terrible pain. The same patient may suffer in one attack more anguish than pain and in other attacks more pain than anguish. Or, either pain or anguish may be entirely absent in any attack in the same patient. In some patients only the pain occurs and the horror never develops and this even in elderly people. In false angina, the conviction that death is undoubtedly near does not come to the sufferer, but there is a terrifying fear that the pain may be that of angina and if so, that death may occur. These patients are afraid of the idea of angina pectoris lest they suffer sudden death.

There is a widespread idea among the profession that the attacks of angina are dependent upon the height of the blood-pressure. Nothnagel's angina vasomotoria is based on this idea in which the spasm of the peripheral vessels becomes so great that the heart, unable to overcome the pressure in front of it, suffers from an attack of pain. The relief by the nitrites has been laid to the reduction of the blood-pressure. Mackenzie reports a case with a blood-pressure at 190 in which he stopped the anginal seizure by giving amylnitrite and some minutes later he found the blood-pressure to be 200. The author has taken blood-pressures in attacks of true angina and found them to be between 130 and 140, which was the height that had been found in the patient the day before the attack and for some weeks previously. Vasquez and other observers report the occurrence of the anginal symptoms in patients with high, low or normal blood-pressures. The blood-pressure itself is, therefore, not necessarily a factor of causation. Patients with high blood-pressures seem clinically, however, to be in much more unstable equilibrium than those with lower pressures and more easily start the painful reflex into action. Neusser reports the case of a patient who did not show any increased pulse during the intervals nor increased blood-pressure during the paroxysms. He also speaks of numerous cases in which the blood-pressure decreased during the stenocardiac paroxysm. He also reports one case in which the blood-pressure was 90 previous to the attack and equally low during the attack. The attack ceased when, through digitalin and theocin the blood-pressure rose to 110 but the dyspnea and cephalalgia persisted. Neusser explains the difference as depending upon the localization of the vascular spasm; if this involves the regulating splanchnics, a marked increase in the blood-pressure may take place. If, however, it is localized in the thoracic region, the paroxysms may be accompanied by a vasoconstriction of the vessels of the upper extremities and of the coronary arteries. If the latter be true, the nutrition of the heart would be reduced and the heart cause a decrease in the blood-pressure.

The patient's face during the attack may be very pale and sweaty, or it may be flushed and as the attack proceeds the vessels of the neck may bulge and throb. Intense sweating may occur over the body and on the hands as well as on the face, and be of great intensity; Osler speaks of one patient's hands being as parboiled as a washwoman's.

Another symptom by no means uncommon is a persistent and distressing hiccup. At times there is a constant desire to urinate and very large amounts of urine may be passed.

Diagnosis.—The differential diagnosis of angina pectoris has two objects in view. The decision, in the first place, of whether or not it is an attack of real angina or of the nervous or pseudo-angina or some allied conditions. In the second place, what is the cause that has set in motion this symptom complex? The sudden onset, the intensity of the pain, the fear of instant dissolution, the lack of dyspnea, the usual slight variation from normal in the pulse, the immobility of the patient and the pinched and drawn expression of the face, make a characteristic picture that is strongly impressed upon the mind. But these are typical cases. These attacks may occur at any age and in men and women, but they most frequently occur in men after the middle period of life, the pseudo-angina usually occurring in women, and the history of fear of heart disease and with it the fear of sudden death, is strongly marked in their minds, and they are influenced by the suggestion from having heard of, or having seen some person in an anginal attack, or by the imagination of how it would occur if it were true. One thus sees the picture varied in detail. Dyspnea, fright and convulsive twitchings and a great deal of jactitation or restlessness is more characteristic of the nervous type of false angina and is usually seen in younger men and women than those in whom one would expect to see true angina. However, there may be a true stabbing cardiac pain or precordial pain that starts the appearance of the false attack and when once it starts it may go on to terrified completion. The vasomotor symptom of flushing is more pronounced in false angina. Pallor, coldness and sometimes sweating, occur in both true and false angina. The ashy gray or livid blue is more characteristic of the true angina. Moreover, in true angina, there is an unavoidable, unsought-for conviction within that death is imminent. In pseudo-angina, one is impressed more with the fact that the patient is badly frightened. In false angina it is evident that the patient is afraid to die. In true angina it is not so much the fear of dying as it is the realization that it may not be possible to avoid death. The pain itself in false angina rarely has the agonizing quality of the pain of true angina and it seldom is accompanied by the real spontaneous feeling of impending death. Moreover, in pseudo-angina, rarely does the pain radiate down the arm, but it is more the precordial pain radiating around the heart, while only in the true angina is the pain of vise-like constriction holding the chest. Sometimes false angina is accompanied by a nervous chill. The false attacks, moreover, are preceded by flushes or feelings of oppression and they may be preceded by various nervous phenomena. In true angina the onset is almost always sudden and can be traced to some definite exertion, emotion or indiscretion of eating, while the attacks of pseudo-angina are rarely excited by effort and are more apt to occur spontaneously without sufficient cause. They may be said to occur more from emotional causes and less from physical effort than the true angina. True angina occurs at night, waking patients

out of a sound sleep. False angina does not and one is justified in saying that it is a symptom complex of the hours of waking consciousness. In listening to the heart in the nervous form of anginal pain, one is more apt to hear mitral murmurs or fairly good cardiac sounds and good rhythm, or, at most, occasional extra-systoles. Both the first and second sounds over the aorta may be exaggerated. In true angina one is very apt to hear a ringing, drum-tap second aortic sound due to the fusion of the three layers of the aorta from an old aortitis or an old syphilitic involvement of the vessels. One is more apt to hear the two aortic murmurs or make out by percussion the dilatation of the aorta. One frequently hears in the subjects of true angina the fetal rhythm of evenly spaced and even value to the heart sounds of chronic myocardial brown atrophy, or the gallop rhythm of myocardial fibroid replacement. The radiation of the pain is an excellent means of differentiation between the pain of real angina and many kinds of precordial pain.

Tobacco causes precordial pain on the edge of the pectoral muscle situated usually about the nipple. Intercostal neuralgia, in which the intercostal nerve is painful and tender is often thought to be angina by those possessing it. In those who have cardiac disease, precordial pains not uncommonly come and go, but they do not take the paroxysmal form of anginal attacks. In chronic alcoholism there is often a persistent precordial pain with tenderness of the pectoral muscles. The pain of angina is, as we have already said, substernal and while its radiation may be unusual, the fact that it radiates from its point of occurrence in the chest out into the cervical and dorsal segments of the cord, is indicative of real angina. Pain following walking against the wind, or exertion, appearing in the arm rather than in the chest, relieved on cessation of effort to reappear when effort is again begun, or accompanied by globus and relieved by eructation of gas and this phenomenon repeated, should cause one to think of real angina rather than to discard this diagnosis. Anginal attacks following syphilitic infection or following influenza should not be considered of false character. The pain of herpes zoster cannot always be differentiated from the pain of true angina, for Neusser reports a case where herpes zoster developed in the upper extremities after an attack of real angina. This is also true where there is hyperalgesia of the skin, which has been known to be left following a case of angina. The persistency of the pain and the tenderness in the skin over more or less wide areas after a few days clear up the diagnosis even before the characteristic rash and vesicles appear. Neusser states that "phrenic neuralgia is observed in many forms of diaphragmatic pleurisy, in pericarditis, in aortitis and dissecting aneurysms and is characterized by dyspnea, later by singultus, sensations of constriction at the insertion of the diaphragm and at the neck and frequently by the radiations of the pain to the left arm." Differential diagnosis would depend upon the physical signs of the pericarditis and the pleurisy and fever. It should not be forgotten, however, that true cases of angina pectoris in the early stages of pericarditis are rare, but occur, as reported by several observers. Many cases reported have been

in reality instances of coronary thrombosis in which the anginal attacks have occurred and a day or two later a pericardial rub has been recognized. The anginal symptoms have been attributed to the pericarditis and not to the real cause, the coronary thrombosis.

Complications and Sequelæ.—Angina pectoris is not a disease. The symptom complex of angina may, therefore, be said to be more a complication of other diseases than to have complications of its own, and the same may be said of its sequelæ. It is a complication of coronary thrombosis or of aortitis caused by rheumatism, by influenza or by syphilis. It is a rare complication of an acute pericarditis and is sometimes a sequelæ of a former pericarditis when old adhesions pull on the origin of the aorta.

Association with Other Diseases.—Trousseau claimed that angina was associated with epilepsy, believing that there was a close relationship. Osler quotes Richardson also as comparing angina pectoris with epilepsy. Cases have been reported in which patients had both angina and epilepsy, one peculiar case being reported by Osler, in which there was a very marked aura of the epileptic, well-marked pain and the sensation of impending death, but the patient did not connect the two in any way and they were recognized in his consciousness as occurring separately.

Persons who suffer from attacks of angina pectoris may naturally acquire other diseases but there is no regular association to the attack of angina except with the groups of diseases which cause infection, with morbid changes in the aorta, coronary arteries and infections or degenerations of the myocardium. When once the foundations are laid which set in motion the reflex of the anginal complex, then disordered functions of digestion or of the kidneys may be the active agent in starting the anginal mechanism in motion.

Clinical Varieties.—True angina may well be separated, as was done by Elsner, into the large and small attacks. The large attacks arise suddenly, usually after exertion, worry or a heavy meal. In these the pain is intense with wide radiation, and the sense of impending death weighs heavily upon the patient. Probably the majority of patients seen in angina suffer from small attacks suggesting severer paroxysms or the possible development of them. These minor attacks are definitely less severe and the pain is definitely less. At times they lack the sense of impending death but at times it is present to a greater or less degree. If the morbid conditions have continued for some time, these slight attacks are apt to occur on slight cause. They are of short duration, however, and in the majority of cases cease promptly with rest. The pain rarely radiates beyond the left shoulder. It is not apt to go into the root of the neck or the throat. In one patient, the author has seen a small attack consist of a single terrific sharp shoot of pain in the great occipital nerve from the nape of the neck up to the top of the head. In these patients at times, in both the severe and minor attacks, the numbness in the arm and the inability to use it is noticeable. As long as the numbness persists, any use of the arm may bring on increase of

pain or the return of an anginal paroxysm, the numbness being felt after the real attack has subsided. The substernal pain usually subsides first, the pain in the arm more slowly, and the numbness of the arm may persist for a day or more. One small attack may be the forerunner of the severest attack, but the patient may go for years with small nagging attacks before the severer ones develop.

Besides the major and minor attacks, individuals vary clinically in their manner and areas of manifesting the clinical evidences of the same pathologic lesions underlying the symptoms. There is a certain wide variation within normal limits of vascular distribution and nerve supply to the same viscera or to the different areas of the body. One spinal nerve or efferent sympathetic may in the majority of individuals go to a certain area, but in other individuals the same area may be supplied by another nerve which, when involved in the morbid process, will present quite a different clinical picture. The aortic plexus receives nerves from the upper cervical, upper and lower thoracic nerves, and their distribution on the aorta may vary, or the area involved may equally vary and produce pain in the neck or arm or downward in the back or legs, depending upon the sensory and efferent arc stimulated. In the author's experience, however, paroxysms of anginal pain from aortitis very commonly radiate the pain upward into the neck and throat and the intense constricting crushing thorax pains seem also to come with the involvement of the aorta rather than of the heart itself. The pain of aortitis is also more distinctly substernal and less commonly precordial.

When thrombosis of the coronary arteries takes place there may be intense paroxysms of anginal pain radiating in its characteristic manner down the left arm. Or there may be no pain. When the symptom complex of angina does appear in coronary thrombosis, the essential clinical peculiarities, as described by Libman, are the rapid pulse, a sudden fall of blood-pressure, a leukocytosis, and in twenty-four or thirty-six hours the appearance of a pericardial rub over the involved area of the heart. Later, if the circulation to either left or right bundle be involved, the characteristic bundle defect in the record of the electrocardiogram will show itself. Often, as the heart recovers itself, there will be present the galloping rhythm of the heart sounds which will often persist for months after the attack. In these attacks of coronary thrombosis, dyspnea, sometimes to a distressing degree, and often cyanosis with rapid pulse rate are present and the cardiac sounds are feeble. Herrick of Chicago divides these cases into four classes: Sudden death in pain; angina with death in a few minutes; non-mortal attacks with slight angina from the obstruction of a small branch; and severe forms fatal after a long period. Allbutt draws attention to the character of the anginal pain in the thrombotic cases as being in kind and intensity and in position of substernal, epigastric or submammary the same as in other forms of true angina, but the pain here is more continuous and occurs less in paroxysms.

ANGINA SINE DOLORE.—Gairdner first described the form of the anginal complex in which real anguish of spirit and the conviction of

instant death but no pain is present as *angina sine dolore*. The other accompanying symptoms of usually normal pulse, absence of dyspnea and death in one of the paroxysms were present, the attacks being analogous to the true angina, only dissimilar in their absence of pain.

PSEUDO-ANGINA.—Another variety is *pseudo-angina*. This is very apt to develop more frequently in women than in men, and in younger than in older people. Also it develops in those who have had friends or relations die of angina or of heart disease, or who, through some reason or some statement made to them because they perhaps possess a cardiac murmur, are convinced that they have heart disease (which to them means sudden death). And again it may develop in patients who have some other form of pain in the precordium. The pain in true angina is substernal near the xiphoid or up near the third rib, but in pseudo-angina it is more apt to be in the mammary line in the fold of the pectoralis major. Hyperalgesia may remain in the skin in both true and false angina. Attacks of pseudo-angina, when they come, are usually accompanied by nervous manifestations beforehand. They do not come suddenly, they do not follow physical exertion, but are apt to follow emotional strains. Patients are more apt in these attacks to have clonic convulsive spasm or develop a nervous chill. They are apt to have flushed faces while their extremities are cold, but in true angina there is more apt to be the real sweating. There is apt to be dyspnea and rapid pulse in false angina. The weak and feeble or irregular pulse belongs to the true angina. In pseudo-angina patients do not die.

TOXIC ANGINAS.—Toxic anginas are most frequently brought on by tobacco. As Osler points out, the disproportionate amount of angina pectoris in nonsmokers in ratio to those who smoke to excess is striking. There are a large number of persons in whom tobacco causes a precordial pain, but this pain does not go to the severity of an anginal attack nor does it become substernal or radiate in the usual way. Patients, however, who suffer real angina increase the number of their severe attacks by the use of tobacco. The author had one patient come to him with intense pain in the chest at the area of the third or fourth rib on the left side which did not radiate to the arm. Upon walking up stairs or up an incline, intense pain would be brought on with a sense of suffocation and a sense of tightening of the chest; there was no dyspnea but the fear of death was distinct. There were no physical signs of cardiac disease. This patient was a stout, active man about forty years of age and a great smoker of cigarettes. He was advised to cut off his cigarettes as they seemed to be the cause of his attacks. This he did and improved greatly. He kept away from them for many months and his attacks disappeared. On going back to his tobacco his pains and attacks of suffocation returned and the patient dropped dead while walking in the street. Two other patients who had attacks of real angina were warned that the smoking of cigars increased their attacks of pain and were asked to desist. This they did and improved. On taking up their smoking again, their attacks quickly returned with fatal results. One

of these patients had been practically free from his attacks for a year, the other for two or three months. The latter patient had gone salmon fishing, and had refrained from smoking until one day he insisted on doing so; but it was noticed that he dropped his half-finished cigar overboard and turned pale but said nothing regarding any pain. Shortly afterwards, while walking the few hundred yards to the club house, he dropped dead without warning. Osler reports a case in which the patient had severe pain radiating down into the left arm. There was no sense of impending death. There seemed to be no organic disease of the heart. This patient showed a distinct causal relationship between the amount of smoking and the amount of pain. He also showed a form of suffocation or choking coming on at night on which Huchard lays great stress as occurring in those suffering from tobacco angina. These attacks are also not uncommon in non-smokers. Such a patient wakes suddenly, particularly just as he has dropped off to sleep. There is a sense of inability to breathe, of choking and the patient sits up striving to obtain air. There is no pain or increased action of the heart. The larynx feels as if it were shut tight and the instant any endeavor is made to bring any air through, it seems to close entirely. This may last for a few seconds or longer and the patient gradually recovers his breath and after the spasm relaxes goes to sleep again. At times these attacks bring with them a sense of helplessness and certainty of suffocation. If the patient will sit up and hold the head back between the shoulders, with the chin tipped upwards as far as possible, remain as quiet as he can, and try to breathe slowly and quietly, he will shorten the period of the intense spasm. They are something like attacks of laryngismus stridulus, although there is not usually the crow-like whoop as in false croup.

Huchard describes eight clinical types of tobacco angina. These, however, seem to vary from attacks of true angina in three of his types to various forms of gastric and cardiac poisoning by tobacco, not truly angina pectoris, although they may be present in patients who suffer from the real anginal form. Huchard claims that one form of angina pectoris of tobacco origin often shows a vasomotor type with extreme pallor of the face and dizziness with increased tension in the pulse, tending to syncope with precordial anxiety with or without pain, cold extremities and cold sweating. Anginal attacks caused by tobacco often become very distressing both in the intensity of the pain, its radiation and the intense conviction of impending death, for these paroxysms in many instances do not differ clinically from severe angina from other causes. The attacks may be provoked equally well by exertion. However, particularly in tobacco angina, one observes the incomplete and abortive attacks consisting of dyspnea with a slight precordial anxiety or simply a substernal discomfort and a sensation of the stopping of the heart and imminent death. Harlow Brooks emphasizes the fact that in the tobacco angina the pulse is frequently arrhythmic and intermittent, the neuromuscular system of the heart being evidently more commonly poisoned in this variety than in the paroxysms usually

encountered. All observers agree that the toxic effects of tobacco on the cardiovascular system are evanescent and quickly disappear as soon as the use of tobacco ceases. This is true when the poisoning has been only functional, and is true in the large majority of instances. Huchard and other French clinicians claim that there is an arteriosclerosis of the aorta and coronaries produced by nicotin and if this be present the anginal attacks do not disappear on the withdrawal of the nicotin but are tenacious and disappear but slowly or may be permanent and warrant treatment with iodids. It is still a moot question whether or not nicotin does produce in man aortic arteriosclerosis extending into the coronaries. The cases usually so diagnosed may well be of infectious origin in the aorta and rendered more severe by tobacco.

Judging from the experience in this country where tobacco is so freely used, one sees but seldom the pure organic tobacco angina of Huchard. One sees the various forms of arteriosclerosis in those who use tobacco and one sees the functional type more than the intense forms of angina. There is no question in the author's mind but that tobacco in those who have anginal attacks due to aortitis or other causes, increases both the intensity and frequency of the severe attacks. The author is convinced that he has seen a few deaths produced by tobacco in those who suffered from anginal attacks, both the painful angina and the *angina sine dolore*. The tobacco seems to add to the danger of tissues already diseased and can, of itself, produce functional poisoning which in turn causes the anginal symptom complex, the latter disappearing very quickly on the cessation of the poisoning.

ABDOMINAL ANGINA.—One distinct clinical type of angina pectoris is that in which the pain begins in the epigastrium and radiates back to the spine, or else it may begin in the epigastrium and become substernal in the middle of the sternum. Osler attributed to Leared the credit of the first description of the angina abdominalis as a well-recognized clinical variety. Heberden describes it as a deviation from the regular type, more as a variation of the symptom, but mentions it distinctly. Potain describes it as angina subdiaphragmatica; and Huchard and Neusser, as angina pseudogastralgica. All authors mention the intensity of the pain, the liability to deception in the real character of the attack and the difficulty of the diagnosis under certain circumstances. Verdon has particularly laid stress upon the form of angina in which the reflex starts from the tension produced by the distended stomach. The patients usually complain of a sense of globus, of a desire and inability to get rid of gas and complain of the flatulency as the cause of their pain. Verdon mentions many cases in which globus arose whenever exertion was made, especially after meals, but when the patient stopped and rested the gas was expelled and the pain stopped instantly, to return, however, in some patients, with the renewal of the exertion of walking. Unless relieved, the attacks may go on to the most intense pain accompanied by the reflex pouring of saliva into the mouth, by the typical pale and drawn face and sweating, by the intense feeling of weakness, and by the fear of sudden death. Verdon claims that unless

the spasm in the gastric and esophageal musculature can be relieved these patients will often die, even though the attacks seem slight in their beginning. The pulse in this form of angina is usually slow and full until just at the end when the full vagal inhibition comes on.

Treatment.—One must separate the treatment of the attacks themselves of angina from the treatment of the patient between the attacks to prevent the recurrence. Many patients are instantly relieved of the pain of the attack of angina by the administration of **nitroglycerin** or of **amyl nitrite**, or **sodium nitrite** as recommended by Lauder Brunton for the treatment of this symptom complex. It has been the author's experience, however, that in some patients, especially in those with low tension pulse, the nitrites may fail to give relief. One patient, an eminent physician, who, suffering intensely from an attack of angina, took nitroglycerin, declared that it increased the intensity of the pain rather than relieved it. Another physician has informed the author that in his attacks of angina pectoris the swallowing of a good mouthful of **whisky** will relieve him quicker and better than glonoin. **Aromatic ammonia** with or without **Hoffman's anodyne** and with or without 1/100 or 1/50 grain (0.00065 or .0013 gram) of nitroglycerin is often an excellent remedy to relieve the pain and spasm. In severe, prolonged and resistive attacks, inhalations of chloroform have been found valuable. **Benzyl benzoate** has been recommended but it is of questionable value. **Morphin** hypodermically is often necessary and will relieve the pain and ease the reflex which the vagus is exerting on the heart, for with it the pulse improves in force and frequency even when it has been slow and weak. Livingston recommended some years ago, hypodermic injections of **ergot**,* declaring that it relieved the pain in angina pectoris. The author has given this drug intramuscularly in several sharp attacks of angina and with excellent success. It has been successful in those cases in which the glonoin did not relieve the pain. **Atropin** is recommended to cut off the vagus irritation on the heart and is spoken of very highly by many who have tried it. Small doses of **adrenalin** have been of assistance in dilating the coronary vessels in the heart or stimulating the accelerator to overcome the vagal reflex. In the abdominal forms of angina, Verdon reports that in one patient practically moribund, he had the courage to pass the **stomach tube** into the stomach and relieved him of a mass of fluid from this viscus which brought the patient back to life and comfortable existence in a few minutes. In the severe forms of pseudo-anginal attacks, full doses of Hoffman's anodyne with ammonia and **ammoniated tincture of valerian** are very effective. This and hypodermic injections of **strychnin** and **Livingston's solution of ergot**, 20 to 30 minims (1.25 to 1.90 c.c.) doses, often prove effective. Recently, in a patient suffering from anginal pains brought about by the throbbing of an aortic aneurysm, great relief was soon obtained by doses of 5 minims

* Livingston's solution of ergot is made by dissolving one drachm (3.75 c.c.) of the solid extract of ergot in one ounce (30 c.c.) of sterile distilled water and filtered, then adding 3 minims (.18 c.c.) of chloroform and 3 grains (.195 gram) of chloretone. Dose, 15 to 30 minims (.92 to 1.9 c.c.) hypodermically.

(.3 c.c.) of the **tincture of aconite** to quiet the over-pounding of the heart action. This also tends to lower the rise of blood-pressure.

Between attacks the difficulty of diagnosing the source of the reflex producing the attacks influences greatly the line of treatment to be decided upon. In youthful cases arising from syphilitic infection there is no question but that the syphilis should be actively and immediately treated. The best treatment of this is some form of **arsenic** intravenously, but this should not be given in large doses but in small doses frequently repeated. For example: one-eighth or one-quarter, at most, of the usual dose of an **arsenobenzol** preparation and this repeated in five days, with a week or ten-day interval between these doses, **mercurial inunctions**, or **bichlorid of mercury**, given by hypodermic or by mouth, may be used with effect. Arsenic in many instances, in the experience of the author, has really seemed to relieve the pain of syphilitic aneurysms and of anginal attacks occurring from a syphilitic aortitis. Syphilitic lesions occurring in the blood-vessels are often stated to occur only in the tertiary stages of the disease, but this is an incorrect observation. Harlow Brooks has shown that in aortitis and myocardial involvement the syphilitic lesion occurs not only as a secondary but as an early rather than a late secondary, and the earlier the blood-vessels are treated by anti-syphilitic treatment the quicker will the infection be held in check whether it be producing symptoms of angina or not. Angina due to syphilitic lesions of the blood-vessels has excellent chances of coming to complete recovery if energetically and properly treated. Rheumatic or influenzal aortitis when producing the attacks of angina pectoris should be treated as an acute aortitis or endocarditis of acute infectious origin. One of the best forms of treatment is the intramuscular or intravenous injections of **cacodylate of soda**. These should be given every day intramuscularly and every two or three days intravenously. Billings recommends from 10 to 15 grain (.65 to 1 gram) doses of this drug in a sterile salt solution and has had excellent success in subacute endocarditis. The author has used this method for many years and with success.

Some patients suffering from anginal attacks have also a high blood-pressure, one type of which shows the peculiarity of a high systolic pressure of 190 or 200 and a diastolic pressure of 80-100. This type of high pulse pressure is usually accompanied by evidences of intestinal putrefaction and can be greatly improved and controlled by proper treatment of the intestinal fermentation. If the fermentation seems to be due to the carbohydrate elements of food, the **Bulgarian lactic acid bacillus** in the form of **artificial buttermilk** taken with one half to one teaspoonful of **milk sugar** with each tumblerful of milk—which is Rettger's method of administration—will often diminish the gas and flatulency quickly. The milk sugar increases the growth of the lactic acid bacteria in the intestines and is not absorbed as quickly from the intestines as was formerly supposed. The milk sugar should be taken undissolved. If the fermentation is due to proteid, putrefaction often with excess of indican in the urine, the cultures of the **acidophilus bacillus** are more effective and this bacillus with the aid of milk sugar can be

implanted in the colon and prevent the putrefaction in that region. Another method of controlling the fermentation in the intestines is to give 5 grains (.324 gram) of **salol** and 5 minims (.3 c.c.) of **castor oil** in capsules four times a day. This if persisted in for some weeks reduces greatly the putrefaction and the systolic blood-pressure comes down. If both diastolic pressure and systolic pressure are high, one must deal with the situation with a **carbohydrate diet** and low proteids, as in all probability chronic nephritic lesions are present.

Balfour in his interesting book on the Senile Heart, in dealing with the treatment of those suffering from angina pectoris, recommends the value of a **dry diet** rather than a fluid one and, in fact, recommends restricting the patient to four or five glasses of fluid a day, and this taking into account the small amount of tea and coffee allowed. His four important rules are as follows: "(1) There must never be less than five hours between each meal. (2) No solid food ever to be eaten between meals. (3) All those with weak hearts should have their principal meal in the middle of the day. (4) All those with weak hearts should take their meal as dry as possible."

In keeping the meals as dry as possible Balfour limits the fluids to about 15 ounces a day. If thirst be complained of, 8 ounces of **hot water** may be sipped four hours after each meal or only after the principal meal. This, he believes, helps clear the stomach and does not increase the amount of fluids in circulation. Hot water quenches thirst quicker than cold. Small pieces of **ice** chewed or sucked are sometimes useful, but the water from the melting ice should not be swallowed because it is apt to nauseate if swallowed. Thirst depends in a measure upon the dryness of the pharynx and sometimes a little **lemon juice** relieves it when water does not. The following dietary is recommended: For breakfast, at about 8:30, one small slice of dry toast with butter, 1 soft-boiled or poached egg. Balfour allows a little fish of short fiber, *i. e.*, haddock rather than cod, with from 3 to 4 ounces (90 to 120 c.c.) of coffee with cream and sugar or this may be replaced by an infusion of coca nibs or cream and hot water or cream and seltzer. If oatmeal with cream is desired, not more than 4 or 5 ounces of the porridge should be taken, and this should be taken alone and not followed by tea, toast and fish. The principal meal of the day should be in the middle of the day, and may consist of fish or meat, or fish and pudding, or meat and pudding. Soup, pastries, pickles and cheese are absolutely forbidden. If fish is eaten, it should never be fried, but broiled, steamed or boiled. The meats allowed are chicken, sweet breads or mutton. Vegetables are limited to a single potato, a little spinach or string beans. The desserts allowed are such as custards or simple milk puddings, such as rice or custard puddings. Ripe fruits can be taken and during the meal four or five ounces of hot water may be sipped if desired. Tea, four or five hours after the meal, may be allowed but no solid food of any kind, such as cake, crackers, bread or toast, is allowed. Hot water with Liebig's extract can be taken as substitute for the tea. Supper must always be a light meal and be

taken about 7 o'clock. A little fish and potato or toast with butter or some plain pudding or bread and milk compose the meal. At bed-time, 4 or 5 ounces of hot water are allowed.

Patients who are liable to attacks of angina and who are suffering from arteriosclerosis may often go along for many years in comfort, provided that they lead a careful and abstemious life in the matter of eating and smoking. They are, however, balancing on a very unstable equilibrium and a single indiscretion may bring on an attack and the patient may die in a so-called attack of acute indigestion. Many patients learn to avoid the foods which disturb them and make them flatulent. They learn to lead a life in which they cannot hurry for trains, they cannot walk against cold winds, and find it extremely difficult to walk up steady and long grades. It is very noticeable among these patients that if they start out quickly when going to walk, their pleasure is soon spoiled by the nagging pain, but if they begin slowly the heart accommodates itself and many of them can go on for even long walks which give them excellent exercise and keep them in good condition. Damaged hearts should be made to do as much as their muscles will permit without exhaustion and steadily trained to remain in as good condition as carefully graded exercise will produce. Persons given to angina must avoid excessive emotions. They cannot afford the luxury of losing their temper but must perforce cultivate a stoical equanimity. Hunter, who was irascible, declared that he was at the mercy of anyone who made him lose his temper and, as a matter of fact, died from a paroxysm of angina induced by a fit of anger.

A drug very highly recommended in the treatment of angina is **potassium iodid**; it is recommended by Huchard, Osler and others in all forms of arteriosclerosis, whether of syphilitic origin or not. This is best given in small doses over long periods, that is, 5 grain (.324 gram) doses 3 times a day. Osler gives from 10 to 15 grains (.65 to .972 gram) a day, and if this amount does not agree he cuts it down to a smaller amount. Iodid of potassium is the form usually used, but the **iodin sodium** may be used if the potassium salt disagrees. Huchard believes that this drug should be taken from three to four years in daily doses of 15 to 45 grains (1 to 3 grams), until all signs of angina have disappeared for many months, and he believes that definite and permanent recovery is not obtainable except after many years of treatment. The vigorous middle-aged patients are the ones who stand this form of treatment best. Older patients improve more if their general hygiene, their intestines and gastric digestion are carefully watched. If the blood-pressure continues high, nitroglycerin in 1/100 grain (.00065 gram) doses 3 times a day is usually sufficient to assist the circulation to good equilibrium for the work that it has to do. In prescribing this drug, however, 1 per cent. solution is more reliable than the tablets and this should not be forgotten. In some patients **nitrite of soda**, in 2, 3 or 5 grain (.130, .195, or .324 gram) doses seems to hold its effect longer than the nitroglycerin. Many physicians believe that **digitalis** should be tabooed in the treatment of angina pectoris

because of its supposed action in raising blood-pressure. Recent investigations, however, all point to the inaccuracy of this belief. Patients who show edema and failing circulation and who, on exertion, have distinct anginal pains, may greatly improve under digitalis. Huge doses to the limit that one can calculate per body weight of patient are not indicated, but those doses which will add to the tone of the cardiac muscle in the sense of increasing its systolic energy as shown in the increasing vigor of the pulse are best. One may give from 5 to 10 drops of the tincture, morning and night, or three times a day. The best preparation for long-continued use is the powdered leaves in half-grain (.0324 gram) doses made in pill form with extract of **gentian** and given morning and evening over long periods of time. The so-called adrenal residue of Rogers and Beebe, which is a residue remaining in the filtrate after the proteins of the adrenal gland have been precipitated, contains a small amount of **epinephrin**. As prepared, it comes as a black powder, and half a grain (.0324 gram) of this powder mixed with equal parts of sugar of milk in a one-grain capsule every four to six hours will often relieve the nagging anginal pains. In one patient under the author's care during a period of three years, it relieved the pains and greatly reduced the number and the severity of the anginal attacks. The patient was an elderly woman whose health was slowly failing from an ever-increasing arteriosclerosis. This preparation has made many patients comfortable who were suffering from the nagging and painful minor attacks, and it has relieved also the severity of the intense attacks.

Patients liable to attacks of angina should not go around without their remedies which they have found of use to alleviate the attacks. That is, they can mix the amount of water and aromatic ammonia and carry it in a bottle so that it can be poured out instantly and swallowed, or they can carry a small bottle of whisky if this gives them relief, their amylnitrite pearls or their tablets or solution of nitroglycerin. Patients liable to real angina have to learn to do things quietly and to be temperate in all things.

Prognosis.—The prognosis of angina pectoris must necessarily depend upon what is considered the decisive factor in bringing about the symptom complex which we know as angina. In general, the prognosis is in ratio to the severity and frequency of the attacks. A mild attack does not necessarily mean a good prognosis, because a mild attack treated with indifference may quickly be the precursor of a severe or even fatal attack. Angina of syphilitic origin is amenable to treatment and the prognosis is better than in any other form. The prognosis of angina due to influenza is good if the patient has the resiliency of youth to assist him to overcome it. The prognosis in older people suffering from the influenza angina should be guarded. The author has seen 3 patients over sixty years of age who were suffering from angina following an attack of influenza, recover from angina pectoris in the last year, but the prognosis in influenzal infection increases in somberness of its outlook in ratio to the age of the patient. Pseudo-angina has a good prognosis, but the difficulty often arises in differentiating

between the true and so-called false angina. Elsner says of abdominal angina that life may be materially prolonged in most cases, the prognosis depending upon the general arteriosclerosis. In cases of angina with aneurysm and aortic disease, Elsner gives an absolutely bad prognosis. Angina from thrombosis of the coronary arteries is a frequent cause of death; it cannot be influenced by any known treatment and the prognosis depends upon conditions which cannot be calculated. The prognosis of all conditions showing the anginal symptom complex is unfavorable in ratio to the ease in which the attack is produced by seemingly insignificant causes. Elsner also says that it is unfavorable in cases of marked arteriosclerosis, with marked hereditary tendencies, with carelessness of the patient, with unfavorable social conditions, failure to rest and the metabolic faults of gout, diabetes, lead-poisoning and with pneumonia. Balfour states that the less abnormal ties one can find in the heart, the more unfavorable the prognosis after angina has developed.

The prognosis of tobacco angina in the milder functional cases, even if there is intense pain with radiation is excellent if tobacco is cut off. If in the severe attacks of angina, tobacco is continued, it increases the seriousness of the prognosis. Tobacco added to the causative factors of a severe type of angina is a deadly combination.

Pathology.—Angina pectoris is not a disease in itself and has not a characteristic pathology. The most common lesion found in those dying from angina is an aortitis of the first portion of the ascending aorta, due either to rheumatism, or influenza, and most commonly to syphilis. This aortitis has usually extended into the coronary arteries. These arteries have usually been credited with being the primary lesion, but many postmortem reports mention the aortitis with healthy coronaries, and when the coronaries are involved at their origin the adjacent aorta is also implicated in the same morbid process. Other cases have shown healthy myocardium, normal coronary arteries and, at times only, an aortitis, but in some instances even this lesion has been lacking. Other hearts have been found with a thrombosis or embolism of its arteries with or without a softening in the muscles fed by the coronary branch, and here again without an aortitis being present. Other post-mortems have shown normal vessels and normal hearts but with old pericardial adhesions around the root of the aorta. An inflamed condition of the connective tissue of the aorta involving the cardiac plexuses has been found in a few patients dying of angina pectoris. Neusser reports tumors on the vagus and phrenic nerves with normal hearts and arteries in a patient dying from a terrific anginal attack. In the cases of abdominal angina the aorta and its branches have been found in a marked condition of arteriosclerosis. It is evident then that there is no single lesion which is always found. It is equally evident that each lesion to which we have attributed causal relations to the anginal attacks is also found in those who have not suffered in life from the anginal paroxysm. The aortitis is the most frequently present of the lesions, but the definite factor common to all the different lesions which sets in

motion the paroxysm with its fatal vagal inhibition seems at present to be the perversion of the normal functions of the vegetative nervous system expressed in terms of pain and excessive inhibition. But without question we are justified in believing that the disease of the coronary arteries, even though it is not the cause of the reflex that sets the anginal attack in motion, may well be the deciding factor in the fatal issue. We are dealing with factors occurring only during the life of the organism in the reflex actions of the vegetative nervous system, and these do not leave behind them after death traces that to-day can be recognized. They exhibit their force and effect in the perversion of function, but their examination postmortem at present is like looking at the empty, burnt-out shells of last night's fire works.

Historical Summary.—Angina pectoris was first accurately described by Heberden on July 21, 1768, when he read a paper before the Royal College of Physicians on "Some Account of a Disorder of the Breast." Previous to that, both Hoffman and Morgagni had reported individual cases in their descriptions of different kinds of dyspnea but did not separate the peculiar form of angina pectoris as was done by Heberden. In France, Rougnon, on February 23, 1768, five months previous to Heberden's description, in a letter to Lorry, described the death of Monsieur Charles, Captain of Cavalry. Most French authors claim this to be the first description of angina pectoris. Huchard, quoting Rougnon's letter, does not use any expression which described pain as a symptom in the attacks in question. Osler, on the other hand, who had evidently seen a copy of the original letter, quotes several sentences showing that the feeling of suffocation felt by the patient was associated with pain of great intensity and believes that the suddenness of the attack, the pain in the region of the heart, the abrupt termination and mode of death following exertion after a full meal, favor the decision that it was a case of true angina. Gairdner quotes the philosopher Seneca as evidently suffering from this disease, although there is a dispute as to the meaning of Seneca's words. There is no question but that Heberden's description was the first connected description of the symptom complex of angina pectoris, picturing it as a disease. In his description he notes the intensity of the pain, the apparent undisturbed serenity of the pulse, the lack of dyspnea separating it from the cardiac asthma, and the frequent fatal termination. Heberden did not separate the pain from the anguish and fear of death. Latham seems to have been the first to have differentiated the two symptoms. Heberden believed it was a disease due to spasm and that the heart was not involved except late as a part of the fatal termination. Jenner was the first to describe the association of the disease of the coronary arteries with angina pectoris. This was done in a letter to Heberden in 1776, after Jenner had seen the famous John Hunter, who had had his first attack of angina pectoris in 1773, and his second in 1776. Jenner did not publish his letter, as he did not wish that Hunter should know and see his opinion. Hunter suffered for twenty years from angina pectoris and, as is well known, died at a meeting of the Hospital Board of the

St. John's Hospital in October, 1793. Further descriptions of the disease were published by Frothergill, Parry, P. M. Latham, Stokes and other English physicians. Allan Burns, in 1809, was the first to bring forth the theory of intermittent claudication, and John Latham, in 1812, described a form of angina which he called *angina notha*, or false angina. The term pseudo-angina, according to Huchard, was not introduced until 1846, by Lartigue. Lauder Brunton was the first to suggest the treatment of the vascular spasm with the nitrites. Leared was the first to describe abdominal angina and Gairdner first applied the name of *angina sine dolore* to the painless attacks of the angina symptoms. Huchard collected sixty-four different opinions from many well-known physicians as to the cause of angina pectoris. Rougnon and Heberden believed in a spasm of the heart. This was to differentiate it from inflammations. Hunter and Jenner believed it to be due to ossification of the coronary arteries. Parry considered it as a spasmodic condition of the myocardium, a momentary exaggeration of an existing feebleness of the heart. Frothergill thought it to be due to fat in the mediastinum. Stokes explained it as due to a dilatation or obstruction of the right ventricle following a paralysis or weakness of the left ventricle. P. M. Latham considered angina as not a disease entity but a symptom complex. Grinza, Corrigan and Lancereaux believed it to be due to a lesion of the aorta, as aortitis, dilatation, or aneurysms, pressing on the cardiac plexus. Virchow, Cohnheim and Quain believed it to be due to embolism or thrombosis of the coronaries. Contraction or obliteration of the coronaries was supported by Kreysig, Parry, Potain, See, Huchard, etc. Various combinations of spasm, intermittent claudication and atheroma of the coronary arteries have been given to explain the symptom complex of angina, especially by Huchard. Others, like Bouillaud and Bucquy, have claimed that there were two sorts of angina pectoris, one coronary and the other neuralgic or neuritic. Desportes describes it as a neuralgia of the pneumogastric plexus with extensions to the gastric and pulmonary and cardiac plexuses and of morbid processes of the organs to which these plexuses are distributed. Laennec believed it was due to pulmonary and cardiac neuralgias forming two kinds of anginas. Various other neuralgias, neuritis of the cardiac nerves, cardiac ganglia or of the cardiac plexuses have been held to be the cause by different authors at different times. Trousseau believed that angina pectoris was a manifestation of epilepsy. Others have thought that it was due to manifestations of gout in the heart or gout in the aorta or some gouty manifestations of the diaphragm. Others have expressed it as a rheumatic affection of the aorta or the cardiac plexuses. Sir James Mackenzie in his latest writings believes it is due to an exhaustion of the cardiac muscle. In other parts of the same article, he speaks of it as if it were of nervous or vascular origin. Sir Clifford Allbutt believes that it is due to an aortitis except when it occurs as a symptom complex of thrombosis of the coronary arteries. Verdon, on the other hand, believes it to be a neurosis of the various segments of the cord in which the neurons show evidence of inflammatory

processes. Von Neusser, of the Vienna school, following Bamberger, his former chief, believes it is a nervous reflex as the expression of some stimulus exerting its force somewhere in the nervous reflex arc of afferent and efferent nerves which finally find their expression in the vagus reflex.

This short historical review is sufficient to show that from Heberden's time to the present the etiology and pathology of this symptom complex are still matters of opinion and not of demonstration. The diagnosis, the clinical description and the treatment are matters of general agreement in the profession. The etiology and pathology are still matters of general dispute.

SECTION V

DISEASES DUE TO PHYSICAL AGENTS

CHAPTER I

HEAT EXHAUSTION

By L. C. JOHNSON, M.D.

Definition, p. 335—**Etiology**, p. 335:—**Exciting causes**, p. 339—**Symptomatology**, p. 339:—**Clinical History**, p. 339; **Physical findings**, p. 340; **Laboratory findings**, p. 341—**Diagnosis**, p. 341—**Complications**, p. 341—**Treatment**, p. 343:—**Prophylaxis**, p. 343; **General management**, p. 343; **Management of convalescence**, p. 344—**Prognosis**, p. 345—**Pathology**, p. 345—**Historical summary**, p. 346.

Definition.—Heat exhaustion is a disturbance of the heat-regulating mechanism of the body, due to exposure to excessive heat, in an atmosphere with a high degree of humidity, and characterized by collapse, with or without a rise in temperature. In a healthy individual, there is the added element of muscular exertion, or of long hours of strain, mental work, or worry.

Etiology.—In discussing the etiology of this disturbance, it is well to consider briefly the underlying physiological principles of heat-regulation, and the experimental contributions which have been made.¹ The regulating mechanism for heat control is necessarily a complex arrangement, since it has to do with balancing heat production and heat dissipation, each of which processes involves several factors. Yet, in a healthy individual, there is a fairly constant end-result, under all conditions, namely, an almost constant body temperature. Heat production occurs very largely by the oxidative processes in the muscles. There is doubtless some heat generation in the abdominal viscera, but only a small portion of the total calories required are produced here, and the amount so generated is practically negligible. Heat loss is accomplished partially through the lungs, in the expired air, but mainly through the skin, by conduction, radiation, and evaporation of perspiration. These are purely physical processes, and the amount of heat so dissipated depends upon the clothing that is worn, the temperature of the air, the degree to which the air is saturated with moisture, and whether or not the air is still, or in motion.

Government, or balancing of the two processes, is brought about by the heat-regulating or thermogenic center, which is situated in the region of the optic thalami, or corpora striata. Whether or not there is a single center, or several closely related centers, is a matter for discussion, but is clinically of slight importance, since the relation between them is so intimate that they act as one. Barbour² has been able to apply heat and cold locally in the region of the thermogenic center. When heat is

applied, there is diminished heat production in the body of the animal, with increased loss of heat. When cold is applied, there is general increased heat production, and decreased loss of heat. Puncture of this region produces marked elevation of temperature, as has been demonstrated by many physiologists since the time of Claude Bernard. The peripheral mechanism consists of afferent sensory fibers, and efferent vasomotor nerves which, by reflex action through the center, regulate the amount of blood in the capillaries on the body surface. There are also efferent fibers which control the secretion of perspiration. This appears to be an active secretory process, directly under nervous domination. Normally metabolism is increased with muscular activity, and the temperature of the body and of the blood is elevated from 1° to 4° F. (0.55° to 2.20° C.), according to the amount of exertion. Loss of heat is at once brought about by dilatation of the peripheral vessels, by radiation and conduction and, if this loss is insufficient, secretion of perspiration occurs, and the element of evaporation is introduced as a further means of heat loss.

An individual, to be able to endure high temperatures without the elevation of body temperature, must be able to perspire, and external conditions must be such that evaporation of perspiration is possible. Zuntz³ describes the case of a man who had no sweat-glands. On exposure to heat, or when working in hot weather, his temperature rose at once to 102° F. (38.88° C.). The man had discovered, however, that if he wet his shirt from time to time, he was perfectly able to go about his work. This loss of heat by evaporation is evidently of prime importance in all cases of heat exhaustion. Haldane⁴ says that when the evaporation of water from the skin is lessened, the loss of heat is inhibited. He places the limit of man's accommodation to moist heat, when stripped to the waist and sitting, at from 88° to 90° F. (31.11° to 32.22° C.), measured by the wet-bulb thermometer. If the man works, the limit is much lower. At 80° F. (26.66° C.), wet-bulb, there is rise in body temperature in a short time, the pulse becomes rapid, there is profuse perspiration, and exhaustion. Leonard Hill⁵ has stated that high temperatures do not affect the body temperature, so long as loss of heat by evaporation is not disturbed. He considers it especially important that the surrounding air be in motion. In his experiments, young adults were placed in a closed chamber, at body temperature. They very soon became restless, but by starting a small fan, and merely keeping the air in motion, they were able to endure in comfort air which was overheated, moist, and chemically impure. The reports of the various army researches, American, British, and German, all note that men are better able to endure marches and heavy work in the tropics, or in summer, when there is a good breeze blowing.

Loss of heat is also dependent upon the amount of water within the body, which is available for perspiration. The body maintains its fluid supply at a fairly constant level, and a large reserve, which is readily available, is constantly carried within the muscles, according to Hunt.⁶

The percentage of water in the blood is not appreciably lowered, even after the loss of several liters of water as perspiration. He adds that if the reserve is extensively reduced, replacement occupies many hours, and that this delay is of importance. This is a strong argument against drawing on the reserve body fluids by restricting the fluid intake.

The experiments of Woodyatt⁷ are of particular significance. He discovered that, by dehydrating animals by large intravenous doses of glucose solutions, it was possible to produce definite rigors, with fever as high as 108° F. (42.22° C.), which was relieved by bringing the body weight back to normal by the administration of water. It was not necessary for the fluids to leave the body, as the same results occurred if the fluids were fixed within the body by salts or protein. He could change the degree of fever at will, by changing the water level.

The amount of water lost is astonishingly large. In men exposed to the sun, either at work or at rest, at Aldershot, it was noted⁸ that 4 men lost on an average three pints of water by perspiration on a march of seven miles. A man lying in the sand can lose 280 grams (266 c.c.) of water an hour by perspiration. It seems probable that in every case of heat exhaustion, there is a large initial loss of water (Aron⁹, Wooley¹⁰). This depletion of the fluid reserve has a definite influence upon metabolism in general.

Heat exhaustion occurs in the greatest number of cases in the hot season of the year, but it may occur at any time, if an individual is exposed to heat associated with a high humidity, as is the case with cooks, laundry workers, stokers, and steel mill operatives. It is most common in low lands, which lie close to bodies of water, where protracted periods of heat occur, accompanied by high humidity, as for instance the Mississippi valley, the regions about the Great Lakes, and the eastern and southern sea-coasts. Less commonly cases are reported from higher elevations, and in high altitudes the condition is rare. Most cases occur in cities, where people are crowded together, and subject to unwholesome surroundings, bad habits, errors of diet, and bad hygiene in general. Those who are debilitated or convalescent from a severe infection or operation, are particularly prone to the condition. Moschcowitz¹¹ records several postoperative cases. Chronic organic disease, myocardial or renal insufficiency, prolonged nervous shock, strain or worry, all render an individual less able to withstand heat. The subject is of decided military importance, as in war men may be transported from a temperate to a tropical climate, and forced to unusual muscular activity for long hours in the sun. The natives are naturally better able to endure the heat in these countries, but even some of them succumb. They have, however, a dark skin, and do not need to resort to clothing to protect their bodies from the sun's rays. They perspire more readily and, being clothed scantily, have the advantage of greater surface evaporation.

Alcohol produces a diminished efficiency in temperature regulation, and after large doses of alcohol the normal reactions to heat and cold

are inhibited. Weisenberg,¹² while on duty in the Philippines, observed heat exhaustion only rarely, even among newly-arrived troops, unless they drank alcohol in some form or other, and the reports of all army observers note the incidence of heat exhaustion as running parallel with the use of alcohol. In the cases of 25 patients of Gauss and Meyer,¹³ who were questioned closely as to the use of alcohol, all but one had taken beer during the twenty-four hours previous to attack, and in amounts varying from a few glasses to a gallon.

Of these authors' 158 cases, 85 were laborers, 12, teamsters, 8, carpenters, 4, firemen, 3, laundry workers, 3, housewives, 3, cooks, and 3, clerks. There were 152 males, and 6 females. One hundred and sixteen were in the third, fourth and fifth decades, the majority of them being in the fourth. One hundred and two were foreigners, and only 45 were Americans.

The solar rays *per se*, are seldom an active cause of heat exhaustion. A white man exposed to the sun will suffer a diffuse erythema, later followed by pigmentation. If the exposed area is very large, he may have slight fever and malaise. But in the case of all whites the clothing worn is ample protection against the active rays of the sun, nor are the rays able to penetrate to any vital part of the body. Aron⁹ exposed monkeys to the sun and found that they died if they could not accomplish heat loss. When only the head of the animal was exposed to the sun, with the body protected, the animal showed no ill effects even after long hours. Aron concludes that insolation of the skull of animals is without effect, if the body temperature is kept within normal limits. He adds that in the case of animals devoid of sweat-glands the sun's rays will, by radiation, heat the skin and subcutaneous tissues to temperatures incompatible with life. Finny¹⁴ in India conducted a similar experiment, using rats as subjects, and found that when they were exposed to the sun in still air death occurred, but that if the air was kept in motion, the animals were unaffected. Wanhill¹⁵ studied the temperatures of helmets worn by men exposed to the sun, to discover whether the color of the lining of the helmets had anything to do with the temperatures which developed. He concluded that the principal factor which affected the inside temperature was the ventilation of the helmet. Phalen¹⁶ conducted experiments with 500 soldiers, who were clothed in orange-colored undergarments, and concluded that they were not any better protected against the heat than were the men who wore white underclothing. Chamberlain,¹⁷ and Freer,¹⁸ discussing the sunlight and its various rays, found that the ultra-violet rays were fatal to amebæ and bacilli, but Chamberlain concludes that it is very doubtful whether the actinic component of the sunlight is a factor in the tropical morbidity and deterioration of troops. He also observed that blondes withstood the heat fully as well as the darker skinned brunettes. It is moreover a common observation that the greatest number of cases of heat exhaustion among soldiers and sailors occurs, not while they are working in the sun, but at night or in the rest periods, when

they are in the barracks, or below deck, where the air is moist and still, and the heat stifling.

EXCITING CAUSES.—The disturbance of the heat-regulating mechanism is apparently brought about by a disturbed metabolism, associated with a lowered water level, in which there is retention of some toxic substance. Whether this substance is an acid or of protein origin, is not clear. Where there is increased muscular activity, the general metabolism is stimulated, with increased respiratory and nitrogenous exchanges, and a rise in temperature. If this is not relieved by increased heat loss, there is added excitability, which contributes to a vicious circle. Pembrey¹⁹ draws attention to the fact that the secretion of perspiration is controlled by the chemical composition and temperature of the blood, and that if the nervous mechanism is paralyzed by some toxic substance, we may have increased vascularity of the skin, without perspiration. Wooley¹⁰ believes that, with the initial loss of water which occurs in heat exhaustion, there is a concentration of the colloids of the tissues, and retention in the cells of substances which should be carried off. This may embarrass the cells to such an extent that there is an imperfect splitting of the protein molecule; hence the presence of the toxic portion of the protein molecule described by Vaughan.²⁰ Gordon²¹ also suggests the possibility of such an intoxication. Gradwohl²² believes that heat exhaustion is an intoxication, brought about by substances formed within the body, under abnormal conditions of heat retention. He emphasizes the similarity of heat exhaustion and uremic states. Mayer,²³ working with corals, thought it possible that death resulted from the accumulation of acid, possibly carbonic acid (H_2CO_3), in the tissues, the rate of formation of this acid being commensurate with the rate of metabolism of the tissues. The animals of the same class which have a high rate of metabolism, as measured by the oxygen consumption, are more sensitive to heat, and to carbon dioxide, than are those which have a low rate of metabolism. Mayer²³ believed that death occurring in the case of these animals, at high temperatures, was not due to asphyxia. Maud Menten²⁴ notes an increased hydrogen-ion concentration of the blood, when barometric pressure is low; we should encounter low barometric figures in heated air, both dry or moist, and in moist air when it is not overheated. Sambon²⁵ and Manson advanced the theory that heat exhaustion was due to infection with a specific organism, and termed the ailment *siriasis*. Their contentions have not held.

Symptomatology.—**CLINICAL HISTORY.**—The onset is almost always sudden, but frequently there are prodromal symptoms for a few hours or a few days before an attack. These consist in: general depression, headache, malaise, dizziness, anorexia, nausea and vomiting, diarrhea, epigastric distress, restlessness, insomnia, and great thirst (polydipsia). Convulsions may be present, and the temperature may be normal, subnormal, or greatly elevated. Gauss and Meyer¹³ cite the case of a driver who left his seat perfectly well, leaned over a fountain to get

a drink, and knew nothing from that time until he awoke in the hospital. He had been admitted with a temperature of 110° F. (43.33° C.). Another man felt ill and restless at home, and went walking in the street for relief, where he was found unconscious. Others are found in a state of collapse in their beds. Blair²⁸ records notes on a case as follows:

A woman aged fifty-four complained in the morning of slight malaise. She did her usual work in the kitchen, complained of thirst, and drank large quantities of water. The temperature of the kitchen was 91° F. (32.44° C.). At six in the evening, while sitting in the yard, she was taken suddenly ill. It was noted that her lips were pale, and that the veins of her neck were engorged. She breathed without difficulty, and her pulse was 100 per minute and of good quality. She spoke a few words intelligently, and then became incoherent, restless, irritable, and resisted examination. Her jaws were tightly closed, the pupils were dilated at first, but later contracted, and complete unconsciousness supervened.

PHYSICAL FINDINGS.—The physical findings depend upon the degree of trauma. A patient suffering from collapse, without a tremendous initial rise of temperature, greatly resembles a person in a state of shock. He may or may not be unconscious; the skin is pale, cold, and clammy, and bathed in a profuse perspiration. The pulse is small, thready, and poorly sustained; the temperature is slightly elevated, or subnormal. Respirations are shallow, and there is often sighing. Blood-pressure (systolic) is usually low—90-100 mm. Heart-sounds are faintly heard, and reflexes may be elicited. The patient may usually be rallied from this condition and recover, or, within a few hours, show a marked elevation of temperature. Those who have suffered greater trauma are usually found unconscious, with a temperature well above 105° F. (40.55° C.). In the case of these patients the skin is hot, dry, and flushed. Some are conscious or stuporous, others may be delirious. Convulsions are frequent in this type, and may be tonic or clonic, and general or focal. Frequently a single extremity is involved, or the muscles of the face and neck. The pupils are contracted, but as the coma deepens they may be dilated. The reflexes are dependent upon the depth of the coma, and upon whether or not paralyses exist. In general, as the coma is lessened and consciousness returns, the reflexes also return, the superficial ones at first, and the deeper ones later. The pulse-rate corresponds roughly to the temperature. With a temperature of 110° F. (43.33° C.) or over, the pulse-rate is from 150 to 180, and with continued hyperpyrexia it becomes imperceptible. The respirations also vary with the fever; with a temperature below 105° F. (40.55° C.), respirations are from 16 to 30; above 107° F. (41.66° C.) they are from 30 to 60. Breathing in coma is labored, shallow, and sometimes grunting, or of the Cheyne-Stokes character. Bowel movements are

almost always involuntary. Consciousness returns with a fall in temperature, and this may occur in a few hours, or be delayed for several days. The return to consciousness is frequently followed by a deep sleep.

In many cases, the prevailing symptoms, and main physical findings, are cramps and extreme contractions of the muscles, particularly those of the legs. Edsall²⁷ comments upon the large number of such cases seen among stokers in ships, or workers in metal, and notes that they are frequently described by ship doctors. In cases which he described, there were spasm and twitchings of the arm- and leg-muscles, later of all the muscles, which seemed to be extremely irritable, so that a slight stimulus brought on maximal contraction. This manifestation disappeared in twenty-four hours, and left the patient free, except for exhaustion. He believed that this was due to faulty metabolism within the muscles themselves, and not to central irritation. Weisenberg¹² describes the case of a cook, forty-one years old, with a history of alcoholism, who had such attacks, which never came except when he was at work in the kitchen. He was seized with violent cramps of various groups of muscles, lasting for three or four days, which were so severe that at one time a shoulder was dislocated by the contractions. He had previously suffered an attack of poliomyelitis, the muscles of his left leg showing the usual atrophy, loss of power and reflexes. During his attacks of heat exhaustion, these muscles were involved in the same manner as were those in which the nerves were still intact.

LABORATORY FINDINGS.—The laboratory findings are not characteristic, yet seem to indicate an intoxication of some sort, particularly those of the urine and blood. In 25 cases of Gauss and Meyer¹² the urine of all showed large numbers of hyaline and granular casts on the second day, but albumin was present in only 5 cases. Gradwohl²² noted a marked parallelism between the urine and blood chemistry findings in heat cases, and in those of renal insufficiency. He agreed with Meyers and Lough²⁸ that cases having a high nitrogen retention, as evidenced by a creatinin determination of 5 mg. (0.0770 grain) per 100 c.c. of blood, were usually fatal. The white-cell count in the cases of Gauss and Meyer ranged from 7,200 to 15,000 per c.mm. The spinal fluid studied by Dopter,²⁹ Hublé and Pigache,³⁰ Dufour,³¹ and Römer,³² showed an increase of cells, polymorphonuclear at first, but later mononuclear. The vomitus in a few cases contained blood, and in others there were bloody, mucous stools.

Diagnosis.—Diagnosis is comparatively simple where there is a history of exposure to excessive heat, a sudden onset, and signs of collapse or hyperpyrexia, without other cause. Undoubtedly many cases in which persons are found unconscious, with convulsions or paralyses, in the hot season of the year, and who pass rapidly into deep coma, and die, are diagnosed as cerebral hemorrhage or apoplexy, without the consideration of heat as the first cause. In the case of persons who have been confined to their beds for a long period, and who pass

suddenly into collapse, the diagnosis of heat exhaustion may also be overlooked, and death attributed to some obscure cause which is never clearly determined.

Complications.—The complications are not numerous, and are most often present where the damage has been extreme. Immediately after return to consciousness there is sometimes *disturbance of speech*, and *inability to swallow*. Also for a time there may be *disorientation*, *hallucinations*, and *delusions*. Other patients show a sort of *negativism*, in which the attention may be arrested, but not held. A marked irritability is noted. Reid ³³ mentions *pneumonia* as being a fairly common complication, frequently overlooked. Of 160 cases, he found this disease present in 10.7 per cent., and it was the cause of 20 per cent. of deaths. In cases of individuals suffering from renal insufficiency, where there is but a slight margin of accommodation, or tolerance for trauma, heat exhaustion is undoubtedly the cause of the complete renal insufficiency which ensues.

Sequelæ.—Many individuals show a permanently impaired ability to withstand high temperatures. Others are subject to headaches, vertigo, nausea and vomiting, on exposure to the sun. Impairment of memory, altered conduct and disposition, with mental degeneration, are not infrequent where the attack has been severe. Motor lesions are not uncommon, and there are fairly numerous records of hemiplegia, or of paraplegia. Disturbances of speech do not commonly persist, and ataxia is rare. Out of 435 cases Hiller ³⁴ noted paralyses in 7. Goebel ³⁵ notes as sequelæ: psychoses, neuroses, hysteria, paraplegia, hemiplegia, and facial palsy. Out of 40 cases, Pembrey ¹⁹ noted sequelæ in only 2. One showed absence of perspiration, and the other wasting of the muscles with ankle-drop. Weisenberg ¹² reports the case of a patient who had fever for twenty-two days, and who was admitted to the nerve ward with mania, a month after his discharge from the hospital. He showed a marked ataxia, and his findings were those of a cerebellar lesion. Nonne ³⁶ reported a similar case.

Clinical Varieties.—Several types have been described, but there seems to be little reason for a division into clinical types, since there is a single cause, and since the apparently different forms vary only in degree of disturbance, rather than in origin. It is not uncommon, moreover, for a case to be first seen as the less severely injured type, in which a high temperature later develops. It is, however, true that cases tend to fall into two classes. In one, which has been described as heat exhaustion, the onset is more gradual, and prodromal symptoms are always present; the temperature is seldom above 101° F. (38.33° C.) and frequently normal or subnormal; the pulse is small and easily compressed; the patient is usually conscious; recovery is frequently prolonged, but is complete and with no sequelæ. The second type has been described as heat stroke. The temperature rises to extreme heights, unconsciousness with convulsions is common, and few or no prodromata have been noticed. The pulse is rapid but of fair volume, respirations

are often of the Cheyne-Stokes type, and recovery or death usually ensues within a few hours or days. With this type sequelæ have been commonly noted. It seems probable that the difference is largely one of degree, or that the individual who has rendered himself more susceptible, by errors of diet, or alcoholic excess, presents the more violent picture.⁸⁷

Treatment.—**PROPHYLAXIS.**—Prophylaxis has to do largely with simple hygienic procedures. The **skin** should be **kept clean by frequent bathing**; the **diet** should be **light** and easily assimilated; the **clothing**, **light**, **loose**, and **airy**. **Alcohol** should be **forbidden**, and **tea**, **coffee**, and **tobacco** used very **sparingly**, since all may be vasomotor disturbers. **Extreme fatigue**, **worry** or **anxiety** should be **avoided**, and **heavy work** confined to the **cooler parts of the day**. **Houses** should be **well-ventilated**, windows open and shaded, and **fans** used where possible to keep the air in motion. **Rest** in the middle of the day should be encouraged, particularly for those who are under par physically. The **bowels** should be kept **regular**, and particular attention given to the **water** intake. Other **cooling drinks** may be used, but at least twelve or fifteen glasses of water should be taken in a day. Those who have suffered from an attack should resort to higher **altitudes**, or open places, where the **air** is **cool**, and **dry**. Those who live in cities during a long-continued hot period, should seek to lessen the usual daily tasks as much as possible and seek rest and recreation from the daily wear and tear.

GENERAL MANAGEMENT.—Where hyperpyrexia is present, the first consideration is to lower the temperature; **hydrotherapy** is the one effectual method of accomplishing this result. The patient should be placed in a tub of tap-water, and friction applied to the body; ice should be added to the bath freely, and the temperature taken rectally every minute. When the temperature has fallen to 102° F. (39° C.), which should occur in from ten to thirty minutes, the patient is to be wrapped in sheets, and removed to a bed, which should be located in a cool, quiet, airy place. The temperature usually continues to fall, and may reach as low as 95° F. (35° C.). If there is still elevation of temperature, an **ice-bag** should be applied to the head, and **cracked ice** given **by mouth**. For a temperature under 103° F. (40.45° C.) **sponge baths** may be given, but if it rises above 103° F., the patient should again be given tub baths. **Iced enemata** have been used by some physicians with success, while others consider them of doubtful value. **Stimulants** are employed freely and, as long as emergency exists, should be given hypodermically, or even intravenously. **Caffein-sodium benzoate**, grains 2 to 4 (0.130 to 0.260 gram), should be administered subcutaneously, and repeated every three hours, also **strychnin sulphate**, grain 1/30 (0.0021 gram), and repeated every three hours. It is sometimes of advantage to alternate the two, so that stimulation is received at short intervals. When the pulse is very rapid, **digalen** may be employed, or any digitalis preparation ready for hypodermatic use, in doses of 15 minims (0.92 c.c.) repeated every two to four hours, until 100 minims

have been given, when the dose should be lessened. For intravenous use, a single dose of **strophanthin**, 1/120 grain (0.0005 gram), may be given, but should not be repeated for twenty-four hours. In extreme emergency, injections of **whiskey** or **ether**, 15 minims (0.92 c.c.), may be used, but the action is largely reflex, and they are not to be employed for continued cardiac stimulation. For convulsions, restlessness, or active delirium, **morphin** may be used, but sparingly, grain 1/6 (0.010 gram), hypodermatically, and repeated every three or four hours. **Sodium bromid**, grains 30 (2 grams), and **chloral hydrate**, grains 15 (0.972 gram), may be given by mouth, and repeated every four to six hours; it may also be given in milk per rectum. Where convulsions are severe, sufficient **chloroform** to produce full anesthesia may be necessary. This is sometimes continued for a prolonged interval.

In view of the findings of McKenzie and Le Count,³⁸ repeated **spinal puncture** should be of decided benefit; the interval between punctures must be regulated by the symptoms of the patient. **Antipyretics** of the coal-tar group are of doubtful value, and since the cardiac muscle is always damaged, they are to be avoided. For alcoholics, **whiskey**, ½ to 1 ounce (15 to 30 c.c.), with **paraldehyde**, dram 1 to 2 (3.75 to 7.50 c.c.), may be given, to prevent delirium tremens, and repeated in an hour if necessary.

The diet should be liquid at first, and fluids should be urged upon the patient. **Milk**, **orangeade** and **lemonade**, 6 ounces (178 c.c.), should be taken every two hours, and where the patient is unable to swallow, **proctoclysis**, with **glucose**, and **sodium bicarbonate**, 5 per cent. of each, should be employed, by the drop method. If desiccation is extreme, **normal saline solution**, 13.5 to 17 ounces (400 to 503 c.c.), may be given intravenously, or by hypodermoclysis, administered slowly. Lewis and Packard,⁴⁰ in some of their cases, withdrew from 10 to 15 ounces (295.70 to 444 c.c.) of blood, and replaced this with normal saline. They considered this procedure of doubtful value. Particular attention should be directed toward elimination, and the bowel tract is frequently the only avenue left open. For this purpose **saline cathartics**, or **compound jalap powder** may be used. **Pilocarpin** is not to be used to bring about sweating, and the stimulation of the skin by external heat should be resorted to only in cases where there is no fever. Blood chemistry determinations should be performed, to check up for retention of nitrogen bodies. Where there is no fever, the treatment is largely stimulative. The patient should be wrapped in **warm blankets**, **massaged**, or external heat applied, if the temperature is subnormal. The stimulative procedures outlined above are to be employed, and the matter of elimination watched very carefully. If fever occurs later, it is subject to the same treatment.

MANAGEMENT OF CONVALESCENCE.—In convalescence the patient should have a **light, nourishing diet**, and should be kept in bed until the pulse and temperature have been normal for at least forty-eight hours. He should be cautioned against any exposure to heat, and if possible should spend a period of time **away from his usual surroundings**

and duties. For paralysis and other nervous involvement, **massage**, with **active and passive motion**, proper **exercises**, and **electrotherapy**, may aid in recovery.

Prognosis.—Of the 158 patients of Gauss and Meyer,¹⁸ 63 died, and of these 46 had a temperature of 105° F. (40.55° C.) or above on admission. One hundred and twenty-nine were in a state of coma on admission, and 58 of them died without regaining consciousness. Thirty-five had a temperature of 101° F. (38.33° C.) or lower on admission, and of these 10 died.

Recovery depends upon the extent of trauma, and upon the general condition of the patient at the time of attack. With proper treatment, the number of deaths among soldiers is surprisingly small, while in the case of older individuals living in cities, the percentage of deaths is considerably larger. Gradwohl²² observed that those patients whose symptoms were severe, but whose blood showed a low nitrogen content, recovered, while those who had high retention, died, even though their symptoms were not alarming at the time of admission. The direct cause of death is not demonstrated, but Pembrey¹⁹ believes that it has to do with changes in the nervous mechanism and the heart, or in the respiratory mechanism. Marinesco⁴¹ describes changes in the Nissl substance of the nerve-cells, and Halliburton and Mott⁴² found that the globulin of the nerve-cells coagulated at 42° C. It is possible that death may be due to partial coagulation of these cells.

Pathology.—McKenzie and LeCount,³⁸ in a study of 37 cases which came to autopsy comparatively soon after death, report edema of the brain in 22 cases, edema of the leptomeninges in 9, and of both, in 4 cases. There was marked general passive hyperemia, especially of the brain and lungs, hyperplasia of the spleen, cloudy swelling of the liver, kidneys, and myocardium. The mucous membranes and the skin, particularly over the sides of the thorax in the axillary region, showed petechial hemorrhages. The suprarenal cortices showed the yellow material to be irregular and lessened in quantity; in one case fresh hemorrhages were noted in the substance of the pons, and in another, small softenings of the lenticular nuclei. The spinal fluid in all was clear, colorless, and usually increased in amount. The investigators determined the water content of a series of nearly normal brains, taken from individuals who died suddenly and by accident, and placed the average water content of brain tissue at 80 per cent. In the heat cases of 1916, the water content of the brains varied from 81.16 to 83.78 per cent. but in the few cases of 1917, the water content was slightly above, or below, the normal figure. They figured that, since the brain is enclosed in a rigid case, even a slight increase, of 1 per cent., would be sufficient to subject the brain to considerable pressure. They explained the lessened water content in the brains of the 1917 cases by the fact that there were fewer cases admitted, and that they received more effective treatment in the wards than was possible with such a very large number of cases the previous year. When the brains were hard-

ened in formalin, and examined, the ventricles were found to be enlarged; under the microscope the sections gave evidence of edema, and the blood-vessels were crowded with red blood-cells. The authors emphasize as significant findings the enlargement of the spleen, and the edema of the brain. Senfftleben¹⁸ records the findings of a soldier who died on the march, as follows: The post-cerebral veins were dilated, and full of blood; dural and pial hemorrhages were present. The basal vessels were empty, but the lateral ventricles were full of blood, as were also the vessels of the choroid plexus. Most of the pathological reports do not reveal any more significant findings, and as Pembrey pointed out, some minute work very soon after death should be done, in order to locate the pathological evidence, if it is to be found.

Historical Summary.—In going over the literature it is particularly interesting to note the terms under which the syndrome of heat exhaustion has been described. Until recently the sun's rays themselves have been considered to be a large factor, or a direct cause. "Sunstroke," "insolation," "Sonnenstich," "calenture," "ictus solis," "thermic fever," "siriasis," "heat apoplexy," "heat asphyxia," "heat stroke," "heat prostration," and "Hitzschlag," are terms which have been applied, and they are a fair summary of the events which have been observed, and of the causes to which the disturbance has been attributed. As far back as 1775, important experiments were conducted by Blagden and Fordyce, which have been recorded anew by Pembrey.¹⁹ These experimenters remained in closed rooms, and after a short period of time, took the temperature of the mouth, and of the urine passed. They found they could remain in a room filled with dry air, heated to 239.9° F. (115.49° C.) and remain for fifteen minutes, without any elevation of temperature. They placed water in two jars and poured a layer of oil over the surface of one of them. They noted that the water in this vessel began to boil, while the temperature of the water in the other vessel did not rise above 172° F. (77.9° C.). After staying in a room of moist air, at a temperature of 129.9° F. (54.5° C.), for 15 minutes, they observed that the body temperature was elevated to 100° F. (37.5° C.). These are simple experiments but pertinent, and we find them only in retrospection.

REFERENCES

1. MacLeod, J. J. R. *Physiology and biochemistry in modern medicine*. St. Louis, 1918. C. V. Mosby & Co.
2. Barbour, H. G. Die Wirkung unmittelbarer Erwärmung und Abkühlung der Wärmezentren auf die Körpertemperatur. *Archiv. f. Path. u. Pharmacol.* Leipzig, 1912, lxx, 1.
Barbour, H. G., and Wing, E. S. The direct application of drugs to the temperature centers. *Jour. Pharmacol. and Exper. Therap.* (Bolt), 1913, v, 105.
3. Zuntz and Schumberg. *Studien zu einer Physiologie des Marsches*. 1901, p. 311.
4. Haldane, J. S. The influence of high air temperatures. *Jour. Hyg., Cambridge*, 1905, v, 494.

5. Hill, L. Recent advances in physiology and biochemistry. London, 1908.

Address to the Physicians' Sec. Assn. for Advancement of Sc., Section J., 1912.
6. Hunt, E. N. The regulation of body temperature in extremes of dry heat. *Jour. Hyg.* Cambridge, 1912, xii, 479.
7. Woodyatt, R. T. Studies on intermediate carbohydrate metabolism. Harvey Lectures, 1915-16.
8. Committee on Physiological Effects of Food, Training and Clothing on the Soldier. 2nd and 4th Reports. *Jour. Roy. Army Med. Corps*, 1909, xii, 211; *Ibid.*, xiii, 592.
9. Aron, H. Investigation on the action of the tropical sun on men and animals. *Philippine Jour. of Sc.*, 1911, vi, 101.
10. Wooley, P. G. Insolation; its prophylaxis and treatment. *N. Y. Med. Jour.*, 1914, xcix, No. 24, 1165.
11. Moschowitz, A. V. Postoperative heat stroke. *Surg., Gyn. and Obst.*, Chicago, 1916, xxxiii, 443.
12. Weisenberg, T. H. Nervous symptoms following heat stroke. *Jour. Am. Med. Assn.*, 1912, lviii, 2015.
13. Gauss, H., and Meyer, K. A. Heat stroke; a report of 158 cases from Cook County Hospital. *Amer. Jour. Med. Sc.*, 1917, cliv, 554.
14. Finny, C. M. Sunstroke, or heat stroke. *Indian Med. Gaz.*, 1918, liii, 361.
15. Wanhill, C. F. Factors which may influence the production of heat stroke among the troops on the march. *Jour. Roy. Army Med. Corps*, 1914, xxii, 661.
16. Phalen, J. D. An experiment with orange-red underwear. *Philippine Jour. Sc.*, 1910, v, 525.
17. Chamberlain, W. P., and Vedder, E. B. The effect of ultra-violet rays on amebæ, and the use of radiations in the sterilization of water. *Philippine Jour. Sc.*, 1911, vi, 383.

Observations on the influence of the Philippine climate on white men of the blond and brunette type. *Philippine Jour. Sc.*, 1911, vi, 427.
18. Freer, P. C. The tropical sunlight. *Philippine Jour. Sc.*, 1910, v, 1.
19. Pembrey. Heat stroke. *Jour. Roy. Army Med. Corps*, 1913, xxi, 156; *Ibid.*, 1914, xxii, 629.
20. Vaughan. Protein-split products, in relation to immunity and disease. 1913, Lea & Febiger.
21. Gordon, A. Osler's Modern Medicine. Sec. Edit., 1914, ii, 332.
22. Gradwohl, R. B. H., and Schisler, E. A study of thermic fever, with special reference to the blood and urine chemical findings. *Amer. Jour. Med. Sc.*, 1917, cliv, 407.
23. Mayer, A. G. Is death from high temperature due to accumulation of acids in the tissues? *Amer. Jour. Physiol.*, 1917, xlv, 581.
24. Menton, M. The alkalinity of the blood in malignancy and other pathological conditions, with observations on the relation of the alkalinity of the blood to barometric pressure. *Jour. Cancer Research*, 1917, ii, 179.
25. Sambon, L. W. Not heat fever but an infectious disease. Remarks on the etiology of sunstroke. *Brit. Med. Jour.*, 1898, i, 744; *Ibid.*, 1899, ii, 650.
26. Blair, M. A. Notes on a case of heat stroke, of the hyperpyrexial type. *Lancet*, 1911, ii, 1550.
27. Edsall, D. L. A disorder due to exposure to intense heat. *Jour. Am. Med. Assn.*, Dec. 5, 1908, p. 1969.

Two cases of violent but transitory myokymia, and myotonia, apparently due to excessive heat. *Amer. Jour. Med. Sc.*, 1904, cxxviii, 1003.
28. Meyers, U. C., and Lough, W. G. The creatinin of the blood in nephritis: Its diagnostic value. *Arch. Int. Med.*, 1915, xvi, 536.
29. Dopter. Bull. et mém. Soc. méd. d. hôp. de Par., 1903, xx, 1396.
30. Hublé, M., and Pigache, R. Sequelles nerveuse consecutives au coup de chaleur. *Arch. de Neurol.*, Paris, 1908, ii, 265, 263.

31. Dufour, R. Des resultats de la ponction lombaire dans l'insolation. *Revue neurol.*, Paris, 1909, xvii, 317.
32. Römer, C. Über die Pathogenese des Sonnenstichs. *Monatschr. f. Psych. u. Neurol.*, Berlin, 1915, xxxvii, 85.
33. Reid, W. D. Pneumonia not a rare complication of heat prostration. *Boston Med. and Surg. Jour.*, 1912, lxxvii, 217.
34. Hiller, A. Der Hitzschlag auf Märschen. Berlin, 1902.
 ——— Wesen u. Behandlung des Hitzschlages. *Deutsch. med. Wehnschr.*, 1913, xxxix, 1185.
 ——— Zur Pathogenese des Hitzschlages. *Berlin klin. Wehnschr.*, 1907, xlv, 939.
 ——— Hitzschlag und Sonnenstich. Leipzig, 1917, Thieme.
35. Goebel, A. J. L. Über die Nachkrankheiten des Hitzschlages. Berlin, 1905, O. Francke.
36. Nonne. Akute Ataxie nach Überhitzung. *Deutsch. med. Wehnschr.*, 1907, i, 868.
37. Bram I. The treatment of sunstroke and heat prostration. *N. Y. Med. Jour.*, 1914, c, 570.
38. McKenzie, P., and LeCount, E. R. Heat stroke, with a second study of cerebral edema. *Jour. Am. Med. Assn.*, 1918, lxxi, 260.
39. Norton, H. R. Sunstroke during the summer of 1896. *N. Y. Med. Jour.*, 1897, lxxv, 311.
40. Lewis, M. J., and Packard, F. A. A report of 92 cases of thermic fever treated at Pennsylvania Hospital in the summer of 1901. *Trans. Assn. Amer. Phys.*, 1902, p. 409.
41. Marinisco, G. Recherches expérimentales sur les lésions des centres nerveux consecutive a l'insolation. *Compt. Rend. Acad. d. Sc.*, Paris, 1906, cxliii, 853.
42. Halliburton, W. D., and Mott, F. W. The coagulation temperature of cell-globulin and its bearings on hyperpyrexia. *Arch. Neurol. Path. Lab.*, London Co. Asylum, Claybury, 1903, ii, 727.
43. Lambert, A. Heat stroke. *Ref. Handb. of Med. Sc.*, N. Y. 3rd Edit., 1915, v, 124.
44. McClure, W. B., and Sauer, L. W. Clothing as a factor in the production of heat stasis. *Amer. Jour. Dis. Child.*, 1915, ix, 490.
45. Simpson, R. J. S. Humidity and heat stroke. *Jour. Roy. Army Med. Corps*, 1914, xxiii, 1; *Ibid.*, 1908, xi, 441.
 ——— The solar element in heat stroke, in its physical relations.
46. Ogilvie, W. H. Sunstroke. A heresy. *Jour. Roy. Army Med. Corps*, 1912, xix, 444.
47. Revenstorf. Hitzschlagkranke. *Deutsch. med. Wehnschr.*, 1907, xxx, 868.
48. Senfftleben. Über die Entstellung des Hitzschlages. *Berl. klin. Wehnschr.*, 1907, xlv, 775, 807.
49. Sutton, H. The influence of high temperatures on the human body, especially with regard to heat stroke. *Jour. Path. and Bact.*, Cambridge, 1908, xiii, 62.
50. Van Giesen, I. Pathology of insolation. *Med. Rec.*, N. Y., 1900, lvii, 1134.
51. Weiner, E. Hitzschlag und Sonnenstich. *Wien. klin. Wehnschr.*, 1915, xxviii, 721.
52. Duncan, A. Remarks on some recent theories on the action of heat in the tropics. *Jour. Roy. Army Med. Corps*, 1908, xi, 71.
53. Steinhausen, F. A. Nervensystem und Insolation. Berlin, 1910.
54. Koidzumi. *Ztschr. f. Mil. Aezte*, Tokio, 1918, lxxv, 5, 24.
 ——— *China Med. Jour.*, Shanghai, 1917, xxxi, 336; *Ibid.*, 1918, xxxii, 573.

CHAPTER II

MORBID CONDITIONS DUE TO CHANGES IN BAROMETRIC PRESSURE

By JOSEPH W. SCHERESCHEWSKY, M.D.

Introduction, p. 349—Conditions due to compressed air, p. 350:—Work in compressed air, p. 350; Physical laws to which compressed air workers are subject, p. 360; Respiratory requirements of the body at atmospheric pressure, p. 360; Law of partial pressure, p. 361; Volume of air required in compressed air work, p. 362; Gases of the body and body tissues, p. 362; Description of compressed air illness, p. 371; Cause of compressed air illness, p. 379; Prevention of compressed air illness, p. 397; Treatment of compressed air illness, p. 407; Devices for safety and comfort of workers, p. 411. Conditions due to diminished barometric pressure, p. 412:—Symptoms of mountain sickness, p. 413; Types of mountain sickness, p. 414; Cause of mountain sickness, p. 418; Prevention of mountain sickness, p. 441; Bibliography, p. 443.

Introduction.—The sea of atmosphere surrounding the earth, at the bottom of which we live, exerts a pressure at sea-level of approximately fifteen pounds to the square inch. Because the tissues of the human body are, like water, practically incompressible, and because the pressure of gases in the interior of the hollow viscera and of bony cavities, such as the middle ear and the frontal sinus, is the same as that of the exterior, we are wholly unconscious of this pressure, except when it is demonstrated to us in some fashion, such as in the familiar experiment of the high school physical laboratory of endeavoring to separate two hollow hemispheres from the interior of which the air has been exhausted, or in the practical affairs of life, such as the filling of a hypodermic syringe with solution, the pumping of water from a well, and the like.

Yet in the course of the numberless activities and industries of modern life, man often exposes himself to abnormal conditions which may cause disease, injury or death unless due precautions are taken.

Among these conditions exposure of the human organism to great variations in the barometric pressure may be looked upon as developments of this modern era which are becoming increasingly frequent and which carry with them grave risks as soon as certain limits are exceeded. Man is exposed to greatly increased barometric pressure when working in compressed air, and to greatly decreased barometric pressure when climbing high mountains, in aeroplane flights, and in balloon ascensions.

CONDITIONS DUE TO COMPRESSED AIR

Work in Compressed Air.—The hazards of working in compressed air may be looked upon as a most important occupational hazard, because of the direct danger to the worker, when the needful measures for his safety are neglected, and because the opportunities for injury are increased by the great development of the engineering feats of the day, such as the construction of massive bridges over deep bodies of water, the driving of underwater tunnels, the sinking in watery soil of the foundations for our towering office buildings, the increasing use of the diving dress in salvage operations and to secure pearl and sponge from the ocean floor.

Because bitter experience has shown that exposure to the increased barometric pressure incident to these operations carries with it the risk of acute illness, permanent disability or death, whenever the pressure or time of exposure exceeds certain limits, it is highly necessary to understand the causes of this morbid action, and to know the principles by which they may be prevented or relieved.

The gradual development of work in compressed air, by means of which man penetrates deeply into water-bearing strata, or far beneath the surface of the water, forms one of the most fascinating chapters of modern industrial development.

Workers are subjected to increased barometric pressure in pneumatic caissons, in the driving of subaqueous tunnels, and in the use of diving bells and of diving suits. The following brief description of each of these kinds of work will serve to give the requisite idea for an understanding of the subject of the conditions met with.

PNEUMATIC CAISSONS.—The use of pneumatic caissons is recognized as the most reliable method for the sinking of important foundations or piers, either under water or in water-bearing soil.

The first suggestion for the use of the pneumatic caisson came from Cochrane, the well-known English admiral who took out a patent in 1830 for the use of compressed air in this manner. The first practical application of the method suggested by Cochrane was made by the eminent French engineer, Triger, who, in 1839, sank a coal shaft at Châlons through wet quicksand. He used an iron shaft four and a half feet in diameter and twenty-five feet deep, provided with an air lock at the upper end to permit the workers to enter the interior. Compressed air was forced into the shaft, thus driving the water out. This method was again employed by Triger in sinking a similar shaft through water-bearing strata at Douchy in 1841.

The first instance of the use of this method in bridge-building was at Rochester, England, where Hughes and Cubitt employed a pneumatic caisson. The caisson was sunk at the site of the bridge pier, and when firm soil was reached was used as the foundation for the pier. Since then the method, as applied by Triger, has come into general use.

Generally speaking, a pneumatic caisson is a device for sinking

foundations to firm ground through various distances of water, quicksand, silt and other watery soil. It is a box-like structure of steel, concrete or heavy timbers placed upside down in the location where the foundation for the pier or other work is to be sunk. In this way a closed chamber is formed of which the ceiling and walls are the airtight roof and sides of the caisson, and the floor the soil through which the caisson is to be sunk. The lower edges are usually bevelled, so as to form cutting edges, which aid the sinking of the caisson.

When the foundation is to be sunk in ground overlaid by water, as in a riverbed, the caisson is floated, roof upward, to its proper location. Its lower edges are then made to "land" upon the river-bed by weighting the caisson, the weights (concrete or masonry) being retained on the roof of the caisson by suitable cribwork. As soon as the caisson has "landed," compressed air is pumped into the interior, thus driving out the water. This provides a space in which workers may excavate the soil beneath the caisson. While excavation is in progress the construction of the pier to be supported by the caisson is begun on its roof so that the weight borne by the caisson increases steadily.

The earth in the center of the caisson is removed first, a bench being left along its borders upon which the caisson rests. When this is at length removed and the air pressure in the caisson diminished, the weight of the growing pier drives the caisson a certain distance into the soil. This process is repeated until at length ground is reached which will furnish a firm support to the foundation. The caisson chamber is then filled with concrete, so that it becomes an integral part of the pier.

Air-locks.—In order to allow workers to pass in and out of the caisson, and to provide for the removal of excavated materials, spaces are left in the pier masonry containing shaft provided with "air-locks." These air-locks are chambers, usually cylindrical, either at the top or the bottom of the shafts with doors in opposite ends, one opening into the compressed air space and the other into the open air.

The process of entering the caisson, or "locking in," is as follows: The door leading to the compressed air space being closed, the worker enters the air-lock. The outer door is then closed and compressed air admitted into this air-lock through a valve until the pressure in the lock is equal to that in the compressed air space. The caisson door is then opened and the worker enters. In leaving the caisson, or "locking out," the process is reversed.

In large caissons separate shafts and air-locks are usually provided for removing materials and for the use of workers. In small caissons one shaft does duty for both purposes. Semi-liquid materials, such as silt, sand and mud, are sometimes removed through an iron tube leading out of the caisson, the material then being blown out by the air pressure within, in the same fashion as soda-water out of a syphon bottle of soda.

After the caisson has been sunk to its bearings and has been filled with concrete, the shafts are also filled in like manner. In addition to the shafts and air-locks, caissons are usually provided with several pipes for conducting compressed air, electric current, and telephone wires.

Air-pressure in Caissons.—In measuring the air-pressure required in caissons, gauge pressure is the standard of reference, *i. e.*, the normal atmospheric pressure of fifteen pounds to the square inch is the starting or zero point, the gauge indicating only the excess over normal atmospheric pressure. The excess air-pressure required to keep the water out is proportional to the depth to which the caisson has descended and is approximately fifteen pounds to the square inch for every thirty-two feet of depth of water. The following table shows the excess pressure which must be employed at various depths in sinking caissons:

<u>Depth</u>	<u>Gauge Pressure</u>
10 feet	4.5 lbs.
20 "	9.1 "
30 "	13.7 "
40 "	18.3 "
50 "	22.8 "
60 "	27.4 "
70 "	32.0 "
80 "	36.5 "
90 "	41.0 "
100 "	45.7 "
110 "	50.3 "

In pneumatic caisson work the depth of 110 feet from the surface, which generally requires an excess pressure of approximately fifty pounds, seems as deep as it is practicable to go. In heavy clay soils so great a pressure is not always necessary, since the clay seals the edges of the caissons to air and water. In more porous soils considerable leakage of air takes place at the edges, requiring the continuous pumping of fresh air to maintain pressure. In this way a good circulation of air takes place. In the former instance, while the air-pressure to which workers are subjected may not be so great, still, because of deficient air circulation, the workers may be exposed to stagnant and exhausting atmospheric conditions.

SUBAQUEOUS TUNNELLING.—The driving of tunnels beneath bodies of water has been among the most conspicuously successful under-water engineering feats of recent years. The principle employed is the same as that in sinking pneumatic caissons—*i. e.*, air-pressure keeps the water from entering at the tunnel-head—but the work proceeds in a generally horizontal instead of a vertical direction. Such tunnels are constructed of circular sections of steel, bolted to their neighbors at the end. The tunnel is usually begun from both shores simultaneously, the headings meeting in midstream.

Excavation at the tunnel head proceeds under the protection of a shield resembling in general form a tunnel section, but with a bulkhead containing doors at its forward end through which excavated material is removed into the interior of the shield. As excavation proceeds at the tunnel-heading, the shield is forced horizontally forward by means of powerful hydraulic jacks placed circumferentially between the shield and the last tunnel section. The rear of the shield is closed by an airtight bulkhead containing air-locks for men and material.

DIVING-BELLS.—Diving-bells are cylindrical or thimble-shaped chambers of iron or steel. They are open at the lower end, contain benches or supports for workers, and may be lowered to various depths of water. Light is furnished either by thick glass windows or by electric light. The water is prevented from rising into the interior of the bell by means of air-pressure.

The first diving-suit is said to have been demonstrated before Charles V in 1538, by two Greek divers, who, in the presence of large crowds, were lowered with a lighted torch in the bell in the River Tagus. The torch was still burning and the divers were dry when the bell was drawn up. The diving-bell was further developed by Halley (1717), Smeator (1788), and Renney. While the diving-bell has had a limited use in subaqueous work, the development of the pneumatic caisson and the diving-suit have largely done away with its use.

NAKED DIVING.—Naked diving is still extensively in use among primitive people, in sponge and pearl fisheries. Naked divers are usually trained in their profession from childhood. According to Hill, mothers hold their children under water at an early age in order to develop their powers of resistance.

Considering that the lungs are filled prior to their descent with air at atmospheric pressure, naked divers penetrate to depths which seem astonishing. From sixty to seventy feet is a usual descent. In some instances a depth of from one hundred and twenty to one hundred and thirty feet have been attained.*

In order to reach bottom as rapidly as possible, the diver's descent is aided by using a heavy stone secured to a rope, by which he may also be hauled up. The foot is placed in a stirrup at the top of the stone. Some of these divers use, as aids to diving, horn-clips placed upon the nose to close the nostrils, oiled sponges in the mouth, and oiled wadding in the ears.

The length of time during which they remain under water has often been exaggerated. The usual time seems to be from forty-five seconds to one minute. Hill points out that the temperature of the water influences the time of submergence, it being possible to hold the breath in warm water for a considerably greater period than in cold.

There is considerable difference between the conditions to which the

* G. Musenga reports an instance of a diver who reached eighty meters without the aid of diving apparatus.

VOL. VI.—23.

354 MORBID CONDITIONS DUE TO BAROMETRIC PRESSURE

naked diver and the worker in compressed air apparatus are exposed. In naked diving, while the lungs are filled, before diving, with air at atmospheric pressure only, the entire surface of the body is exposed to the weight of the column of water corresponding to the depth of the dive. At one hundred feet this would be in the neighborhood of



FIG. 1.—DIVER IN DRESS, FRONT VIEW. (Courtesy of A. Schrader & Sons.)

three atmospheres of excess pressure and would result in the compression of the air of the lungs to one fourth of its original volume. From a position of the fullest possible inflation, the thorax therefore would assume an expiratory position, the diminution in volume of the air in the lungs being further facilitated by the ascent of the diaphragm and the compression of the abdomen.

No such diminution can take place in the bony cavities of the middle ear and the accessory sinuses of the nose. There is, therefore, a

strong cupping effect in these hollows, as the air in them is at a relatively much diminished pressure. This accounts for the profuse bleeding at nose, ears and mouth often observed in these divers. The eardrum is often ruptured under the influence of the pressure. When the openings to the accessory cavities of the ears and face are patulous, sea water penetrates into their interior, thus equalizing the pressure to



FIG. 2.—DIVER IN DRESS, SIDE VIEW, SHOWING SHOES, AIR HOSE, TELEPHONE CABLE, ETC. (Courtesy of A. Schrader & Sons.)

a considerable extent. The great difference between the conditions to which the naked diver and the compressed air worker are exposed lies in the fact that, while the external pressures are the same, the compressed air worker breathes air at a pressure counterbalancing that of the water.

DIVING IN DIVING-SUITS.—The diving-suit is the invention of Siebe, who, in 1819, devised the open diving-suit. This consisted of a metal

helmet, attached to a watertight jacket, beneath which a combination suit reaching to the arm-pits was worn. Air was forced by a force pump through a flexible tube connected with the helmet at a pressure slightly in excess of that of the depth at which the diver was working. This kept the water from rising in the jacket, the excess air escaping beneath its edges. This arrangement necessitated the maintenance of



FIG. 3.—DIVER IN DRESS, BACK VIEW, SHOWING AIR HOSE AND TELEPHONE CABLE. Note the lacing of the legs. This is to prevent capsizing of the diver from inflation of the legs of the suit should he be "blown up." (Courtesy of A. Schrader & Sons.)

an upright posture at all times, for if the diver stumbled and fell water filled the diving-suit and quickly drowned the diver, unless he was brought rapidly to the surface.

After further experimentation, Siebe, in 1837, devised the closed diving-suit, which is the one generally adopted. Diving apparatus generally employed in this country consists of seven parts, as follows: (1)

helmet with breastplate; (2) waterproof diving-suit; (3) flexible air-hose, with metallic couplings; (4) leaden weights to be suspended from the back and chest; (5) weighted shoes; (6) life line; and (7) air-pump.

The helmet is dome-shaped and has three windows of heavy glass. Occasionally there is a window in the top of the helmet to enable the diver to look upward. The helmet is screwed to the breastplate by

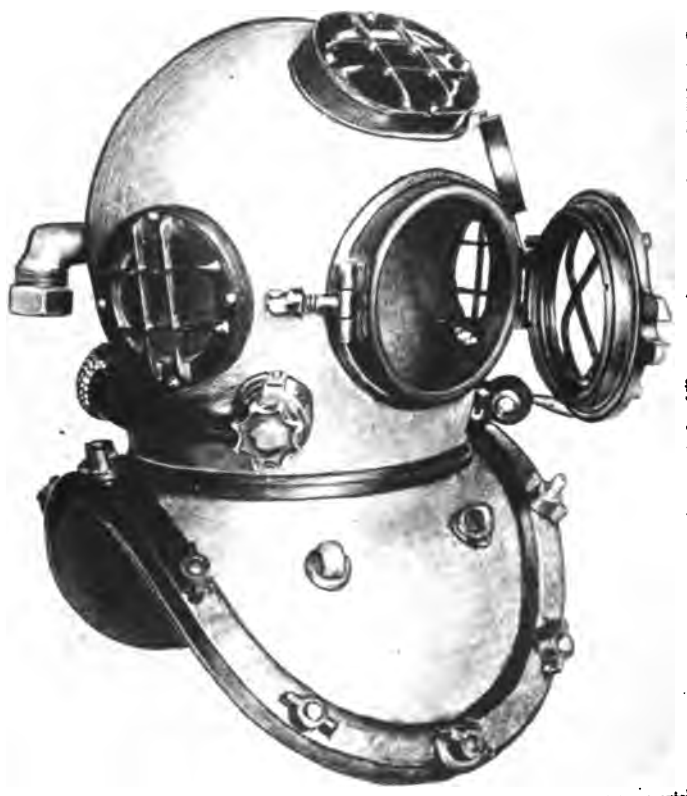


FIG. 4.—DIVING HELMET, $\frac{3}{4}$ VIEW, FRONT. (Courtesy of A. Schrader & Sona.)

means of segmented screw threads, so that a slight turning movement is sufficient to attach or detach the helmet.

The breastplate is secured water-tight to the upper edge of the diving-suit by means of a gasket and clamps.

Air is supplied from the air-pump to the diver through an air-hose through an inlet valve in the back of the helmet which permits air to enter, but not to escape. This is necessary to guard against a sudden escape of air should the air supply be cut off by failure of the pump

or rupture of the air-hose. A sudden escape of air under these circumstances would subject the diver to a fatal "squeeze" in a manner to be later discussed, if he were at any depth. The expired air escapes through an outlet valve which checks in the reverse direction from the inlet valve. The tension of this valve is adjustable by the diver so as to enable him to adjust the degree of inflation of his dress and hence

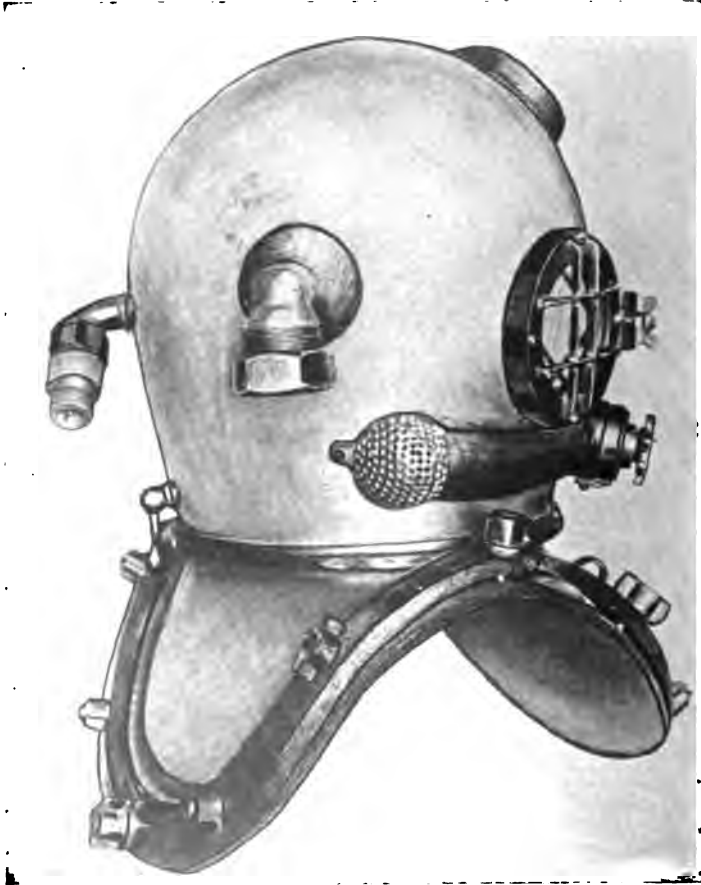


FIG. 5.—DIVING HELMET, $\frac{3}{4}$ VIEW, REAR. (Courtesy of A. Schrader & Sons.)

his buoyancy. It is obvious that the pressure within the helmet must always be equal to the water-pressure outside; otherwise the air would be driven from the suit into the helmet and impede or prevent respiration by pressing on the diver's body. Haldane has shown that a correct position of the outlet valve is of considerable importance. If it is

too high up on the helmet, as the diver enters the water excess air is driven out of the suit through the outlet valve, and the water-pressure on the chest and thorax is so great as to make breathing labored. This is due to the fact that the water-pressure is measurably higher on the lower parts of the body than it is at the outlet valve. Hence, under these circumstances the diver has to breathe from a rigid air-space, the helmet, while the rest of his suit is closely applied to his body. Hence, he can get air only on the instroke of the pump.

On the other hand, too low a position of the outlet valve favors

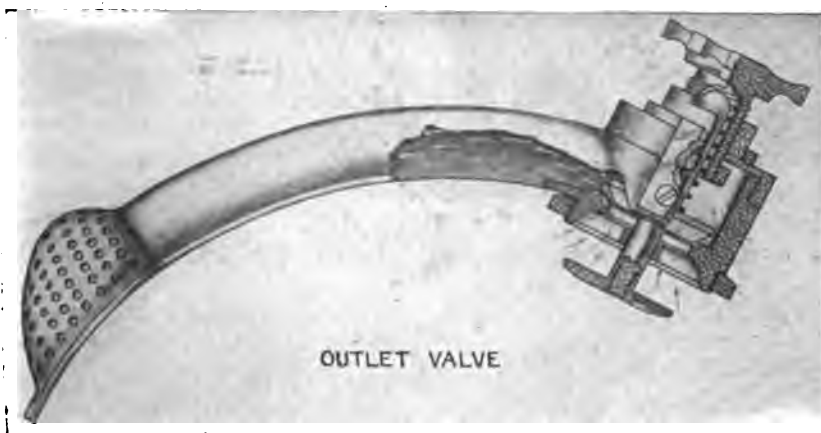


FIG. 6.—REGULATING ESCAPE VALVE. (Courtesy of A. Schrader & Sons.)

accumulation of air in the suit, the helmet will be completely lifted from the shoulders, and the diver tends to rise.

The diving hose is about one inch in exterior diameter and one-half inch in interior. It is usually made in 50 foot lengths with metallic couplings. Diving-hose should be capable of withstanding a pressure of 500 pounds to the square inch. For ordinary diving, air is usually supplied by double-acting air-pumps, manually operated. These are designed, as a rule, to deliver $\frac{1}{5}$ of a cubic foot of air at a revolution. As air becomes hot when compressed, the pumps are water-jacketed. While one pump will supply two divers in shallow water, and one diver at moderate depths, for deep diving the air supply from such pumps is inadequate. Under such circumstances power-driven air compressors must be used, or iron flasks in which air has been stored at high pressure may deliver to the diver through a reducing valve.*

* French states in the salvaging operations of the submarine F-4, in Honolulu Harbor, in which the record dive of over 300 feet was reached, torpedo air-flasks containing air compressed 2,500 lbs. to the square inch were used as a means of air supply, through the medium of suitable reducing valves and an equalizing chamber.

To enable the diver to sink, weights are suspended from the front and back of the chest and he is shod with leather shoes with heavy leaden soles.

In addition, a life-line is provided, usually manilla rope, for the purpose of raising and lowering the diver to and from the bottom. It is also frequently used for transmitting signals, by means of pulls. In the best type of diving-suits, however, means for telephone communication are provided.

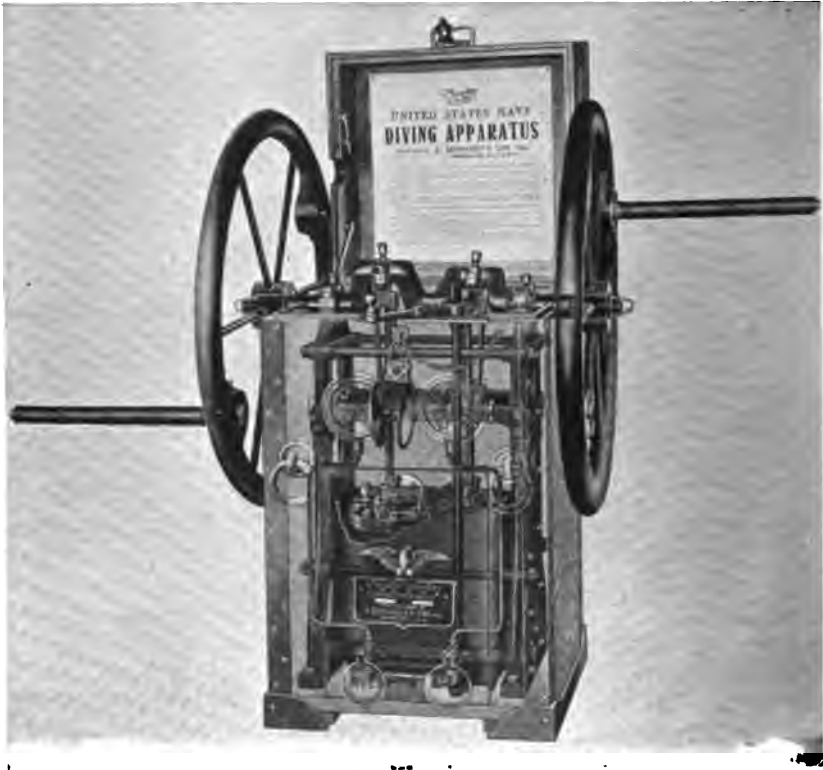


FIG. 7.—DIVER'S PUMP. (Courtesy of A. Schrader & Sons.)

Physical Laws to Which Compressed Air Workers Are Subject.—

It is evident, from the foregoing description of compressed air work, that the physical conditions to which all compressed air workers are subjected are fundamentally the same, and differ from work at ordinary atmospheric conditions only because of the increase in barometric pressure.

Respiratory Requirements of the Body at Atmospheric Pressure.—

It is a familiar fact that air as inhaled in the lungs is a gaseous mixture consisting approximately of 79 per cent. nitrogen, 20.98 per

cent. oxygen and 0.04 per cent. carbon dioxid. The average composition of expired air is 79 per cent. nitrogen, 16.02 per cent. oxygen and 4.38 per cent. carbon dioxid. The air has therefore lost 4.94 parts of oxygen and gained 4.34 parts of carbon dioxid. The discrepancy between the oxygen lost and the carbon dioxid gained is due to the fact that a certain portion of the oxygen combines with hydrogen and forms water.

The total air capacity of the lungs is in the neighborhood of from 4,000 to 5,000 c.c. In normal breathing the tidal air is about 500 c.c. The average resting adult requires about $\frac{1}{4}$ cubic foot of air per minute. This requirement rises rapidly with physical exertion. A man at moderate physical labor requires in the neighborhood of $1\frac{1}{2}$ cubic feet of air per minute.

Before inspired air can reach the air-cells of the lungs it must first pass through and fill the nose, throat, windpipe and bronchial tubes. The capacity of these is about 140 c.c. The ventilation of the air-cells is therefore accomplished for the most part by diffusion between the alveolar air and the tidal air. For this reason expired air, as it issues from the nose and mouth, does not correspond exactly with the composition of the air in the alveoli of the lungs, which contain considerably more carbon dioxid—in the neighborhood of 6 per cent.

Law of Partial Pressure.—The passage of gases in and out of the body is governed by the well-known law of partial pressure. This law is, briefly: If a mixture of gases exerts a certain pressure, each gas of the mixture exerts a pressure proportional to the percentage of the gas present in the mixture. If air is approximately $\frac{1}{5}$ oxygen and $\frac{4}{5}$ nitrogen, it follows that, at the ordinary atmospheric pressure of 15 lbs. to the square inch, the pressure exerted by oxygen is 3 lbs., and that by nitrogen is 12 lbs. In similar fashion, in alveolar air, which contains about 6 per cent. of carbon dioxid, the partial pressure due to the carbon dioxid present is approximately 6 per cent. of 15 lbs. or 0.9 lb.

Observation and experiment have shown that it is the partial pressures of oxygen, nitrogen and carbon dioxid, and not the percentages, which are of importance so far as vital pressures are concerned. Thus, if we progressively rarify air we effect no change in its percentage composition, yet animals will rapidly succumb as soon as the partial pressure of oxygen is reduced below a certain limit. On the other hand, a much lower percentage of oxygen than is normally present in atmospheric air will sustain life if the partial pressure due to the oxygen is raised by compressing the mixture.

In similar fashion the percentage of carbon dioxid present in alveolar air reacts to increases in barometric pressure. If we increase the atmospheric pressure to which we are exposed by going into compressed air, either in caissons or below the surface of water in a diving-suit, the percentage of carbon dioxid in the alveolar air will diminish proportionally to the increase in the pressure. Thus exposure to an atmosphere of 15 lbs. excess pressure, or 30 lbs. absolute, will have the

effect of diminishing the carbon dioxid in the alveolar air from 6 to 3 per cent.—since 3 per cent. of carbon dioxid in a gas mixture at 30 lbs. absolute pressure exerts the same partial pressure in pounds as 6 per cent. at 15 lbs. absolute pressure.

Volume of Air Required in Compressed Air Work.—The need for the maintenance of a constant tension of carbon dioxid in the blood and tissues of the body, and as a consequence in the alveolar air, leads to the following important conclusion (first pointed out by Haldane) in regard to the air supply to be furnished workers in compressed air: The volume of air which must be furnished each individual is the same, measured at that pressure, as would be required by that person at atmospheric pressure, so that at no time will the tension of carbon dioxid in the alveolar air be greater than that corresponding to 6 per cent. divided by the absolute pressure in atmospheres.

Thus, if a diver doing moderate work requires 1.5 cubic feet of air per minute at atmospheric pressure, he will still require 1.5 cubic feet of air per minute while doing work at a depth of 33 feet, an excess pressure of one atmosphere, or at two atmospheres absolute pressure. Since the volume of gases is halved, when the pressure is doubled, 3 cubic feet of air per minute, at atmospheric pressure, must be compressed to two atmospheres absolute in order to furnish an adequate supply.

At four atmospheres absolute pressure, corresponding to a depth of 100 feet, the air-pump must be capable of compressing 6 cubic feet of air per minute; at eight atmospheres absolute pressure or 231 feet depth, 12 cubic feet of air per minute are required. This is a minimum. Where the diver must perform hard work, this standard must be raised.

This conclusion is of special importance to divers in cases in which the air supply must be furnished by pumps, manually operated as a rule. It is not usually of such great importance in caisson work, as so much air escapes beneath the edges of the caisson that a very free air supply is often required just to maintain the required pressure in the caisson. This necessitates high duty air-compressors.*

Gases of the Blood and Body-tissues.—Some discussion of the gases dissolved in the blood and body tissues is necessary in order to understand the effect upon man of variations in barometric pressures. There are three principal gases held in solution, or in chemical combination with the blood and the body-tissues, *i. e.*, nitrogen, oxygen and carbon dioxid. The oxygen and nitrogen are, of course, derived from

* These facts were derived by Haldane in the course of his work for the Diving Committee of the British Admiralty. The extreme panting experienced by divers was formerly thought to be an effect of compressed air. Haldane, however, showed this to be due to accumulation of excessive amounts of carbon dioxid in the helmet, because of inadequate air supply. Until Haldane demonstrated that the volume of air furnished the diver must be the same measured at all pressures, divers were supplied only with the volume of air per minute required by an adult at atmospheric pressure. The fact was lost sight of that, after compression, this volume of air when it reached the diver would be proportionately reduced.

the air while the carbon dioxide is derived from the combustion processes of the body. The two latter gases are present in the body-tissues, not only in the form of simple solution but in chemical combination as well. Consequently, they are found in greater quantity than if present in simple solution, according to the law of partial pressure. Since nitrogen, as a gas, is inert, so far as we know, where the body is concerned, the amount of nitrogen gas found dissolved in the blood and tissues of the body corresponds very closely to the theoretical amounts required by its partial pressure and coefficient of solubility in the blood and body-tissues.

COEFFICIENT OF SOLUBILITY.—The coefficient of solubility of a gas is the amount which can be dissolved by 1 c.c. of any given liquid at standard conditions of pressure and temperature—760 millimeters of mercury and 0° C. (32° F.). This coefficient is naturally affected by the temperature of the liquid, the amount of gas dissolved being less as the temperature rises.*

As the temperature of the body is practically constant, the coefficient of solubility in the body fluids of the various gases noted above is also practically constant. In the case of nitrogen, however, an important exception, as we shall see, must be noted. Vernon has shown that the solubility of this gas is much greater in oils and fats (from five to six times greater) than it is in the other tissues of the body.

The practical effects of exposing the body to increased pressure will be to increase the amount of these gases dissolved in the body-tissues. So far as oxygen and carbon dioxide are concerned, the excess dissolved in blood and body-tissues, under the ordinary conditions of compressed air work, are so small, in proportion to the very much larger amount of these gases present in the body in chemical combination, that they may be disregarded for all practical purposes. Such, however, is not the case with nitrogen. As this is an inert gas, serving, so far as respiration is concerned, as a diluting medium for oxygen, it is present in the blood and body-tissues, according to the law of partial pressure, in amounts proportionate to the pressure and its coefficient of solubility. When, therefore, an individual is exposed to increased atmospheric pressure, a correspondingly greater amount of nitrogen gas is taken up by the blood and body-tissues. If the excess pressure is too suddenly removed, the excess of dissolved nitrogen has no opportunity to be gradually removed through the lungs; hence, it is disengaged in the form of bubbles in different parts of the body, giving rise to the symptoms which will be described later.

RATE OF SATURATION AND DESATURATION OF THE BODY WITH GASES AT INCREASED PRESSURE.—Inasmuch as the skin is a waterproof and practically impermeable envelope, the saturation of the body with gases at increased pressure is accomplished by the lungs through the medium of

* We all know that if water is boiled all the dissolved air in it will be driven off. Also, if water is gradually heated, air bubbles will form on the sides of the vessel before actual boiling takes place.

the blood. The rate at which the body will become saturated with gases at the new pressure, when exposed to compressed air, is governed by the following circumstances:

The blood, as it flows through the lungs, becomes instantaneously saturated with gas at the new pressure. The tension of the gases in the blood, as it leaves the lungs, is, therefore, very much higher than in the other tissues of the body. Consequently, as the blood circulates it will give up gas to the tissues until the tension of the gases dissolved in the tissues is equal to that in the blood. The blood on its return to the lungs takes up a fresh charge of gas which is again given up to the tissues until, at length, the tension of the gases taken up by the body-tissues is about the same as that of the external air.

The rate of saturation, however, is modified by certain variables. These are:

- (1) The rapidity of the circulation.
- (2) The ratio which the volume of the blood bears to the total volume of the body.
- (3) Variations in the coefficient of solubility of nitrogen for different tissues of the body.
- (4) Variations in the richness of blood supply to different parts of the body.

Rapidity of Circulation.—It has been estimated that the average time of a round of circulation in a resting individual is about one minute.* The speed of circulation, however, is greatly increased by physical exertion, so that during heavy muscular work a complete round of the circulation may take place in eight or ten seconds. A man at hard work under compressed air will, therefore, become saturated with gas at the new pressure much more rapidly than when resting.

Ratio of Volume of Blood to Volume of Body.—The ratio of blood volume to body volume is ordinarily given as about 1 to 20. As previously mentioned, however, fatty tissues can dissolve approximately from five to six times as much nitrogen as other body-tissues. Since about 15 per cent. of the body weight consists of fatty tissues, this 15 per cent. has, weight for weight, six times the nitrogen-absorbing capacity of the other tissue of the body. This results in raising the effective ratio of blood weight to body weight, so far as the capacity for nitrogen gas absorption is concerned, so that this ratio, instead of being 20 to 1, is really about 33 to 1. In other words, for the purpose

* Thus, according to Haldane, venous blood entering the lungs contains about 8 per cent. carbon dioxide, while expired air contains 4 per cent. As the expired air loses oxygen to, and gains carbon dioxide from the blood, the volume of air to which the blood has been exposed must be about twice the volume of the latter. Since in quiet breathing 7 liters of air are taken per minute, the volume of blood which has passed through the lungs in that time is in the neighborhood of 3.5 liters. As it is known in other ways that the average person has about 3.5 liters of blood, it is evident that about one minute is required for a round of the circulation.

of calculating the rate of saturation with nitrogen gas at excess pressure, we may regard the blood as constituting only about 3 per cent. of the body weight for this particular purpose. In fat individuals this ratio must obviously be still further increased.

Rate of Saturation.—The rate of saturation and hence the rate of desaturation is of the highest importance in understanding the effects of exposure to compressed air upon men, as it is only by a thorough understanding of the process that the necessary precautions can be adopted. Disregarding for the moment the fact that, because of dif-

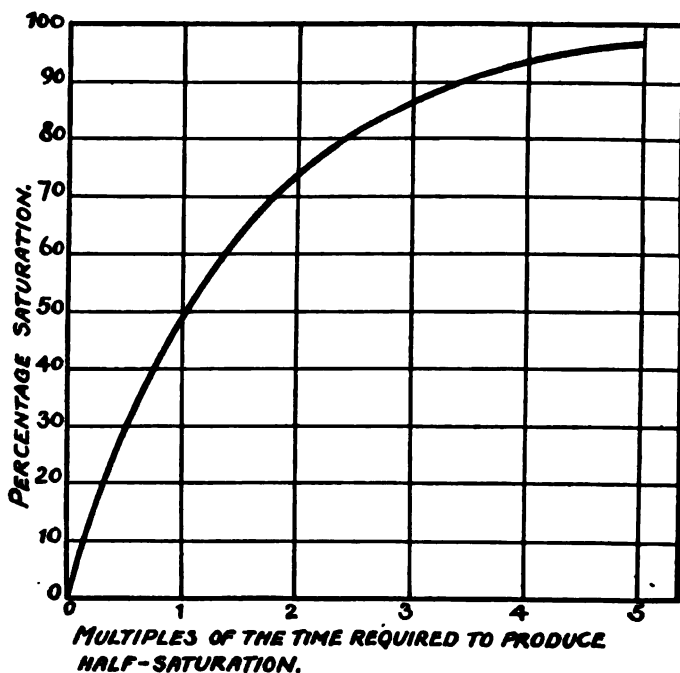


CHART 1.—(According to Haldane.) Assuming a part becomes $\frac{1}{2}$ saturated in 23 minutes, it will be 75 per cent. saturated in 46 minutes, 87½ per cent. saturated in 69 minutes, 93.75 per cent. saturated in 92 minutes, etc.

ferences in blood supply, saturation must proceed at different rates in different parts of the body, the following description of the process will serve to give an idea of the manner in which this is effected:

Assuming, for saturation purposes, that the blood should be regarded as constituting approximately 3 per cent. of the body weight, the process is as follows: During the first round of the circulation the blood leaves the lungs fully saturated with gas at the new pressure.

Because of this difference in tension of the gases in the blood and the tissues, the excess gas is given up to the tissues until the tension in the blood and in the tissues is equal. As the blood forms only 3 per cent. of the tissue volume, at the close of the round of the circulation the blood will be 3 per cent. saturated, and the body 3 per cent. saturated. The blood, on entering the lungs again, is charged to saturation, and again loses its excess to the body-tissues. Since both the blood and the body are 3 per cent. saturated as the blood enters the lungs, it is clear that during the second round the addition to the body-tissues will be 9 per cent. of 97 per cent., or 2.91 per cent.; on the third round, 3 per cent. of 94 per cent., or 2.82 per cent., will be added, and so on in continually smaller increments.

On following out the calculation, according to Haldane, it will be found that the body will be half saturated with nitrogen at the new pressure in about 23 rounds of the circulation, three-fourths saturated after 46 rounds, seven-eighths after 69 rounds, etc. The following curve shows the saturation of the body with nitrogen.

This reasoning would hold if the blood were equally distributed to all parts of the body and the volume of the circulation in liters per minute remained the same. We know, however, that the blood is not equally distributed through the body, the organs and muscles having a rich blood supply while the fasciæ, tendons and fat are only scantily supplied, and that great variations in the rate of circulation take place according to the amount of work performed by the individual.

Physical exertion on one hand will greatly increase the rate at which saturation takes place, while on the other, a scanty blood supply to various parts of the body would cause such parts to lag behind the rest of the system in the rate of saturation.

It is probable that the tissues are over 90 per cent. saturated after five hours' exposure. The rate of saturation is of great importance for the reason that the time of desaturation, other things being equal, will be the same as the time of saturation.

When the body-tissues have become saturated with nitrogen at high pressure, if the individual returned too rapidly to atmospheric pressure, the blood leaving the lungs would become instantaneously desaturated of the excess nitrogen it contained. Important pressure differences will therefore be created between the blood as it returns from the lungs and the tissues which are still saturated with gas at the previous pressure. If the difference in pressure between the gases in the blood and in the tissues is too great, the gases will be released from the supercharged tissues more rapidly than they can be taken up by the blood. As a result bubble formation will take place. Once bubble formation has begun, the bubbles form starting points for further bubble formation. Such bubbles may block the circulation in small blood-vessels, or when formed in nervous tissues may injure it either by mechanical pressure or by interference with the blood supply. Such injuries may be severe.

Fortunately, the highly albuminous body fluids permit a considerable degree of supersaturation with gases before bubble formation will take place. According to Haldane, so long as the tension of the nitrogen dissolved in the body-tissues is not more than twice that in the blood, no bubble formation will take place. There is, however, imminent danger of such bubble formation whenever this pressure difference is exceeded. It is evident from the foregoing, as a general principle, that when an individual passes from a high to a low pressure, the period of decompression must be so managed that the pressure difference between gases in the blood and those in the tissues shall never be greater than 1 to 2.

Effect of Compression on the Worker.—It is only while the pressure is changing that a person under excess barometric pressures feels symptoms. As the gauge rises, there is a sensation of pressure in the ears which may become acutely painful if communication between the rhinopharynx and middle ear is not free. The pain has been compared to the sensation caused by forcibly introducing a stick into the ear canal. It is due to the fact that the air-pressure on both sides of the eardrum has not been equalized. If the communication between the middle ear and rhinopharynx is not speedily opened, a rupture of the eardrum is likely to follow.

Compressed air workers themselves recognize the necessity for a free channel of communication between the middle ear and the pharynx. Beginners are instructed to swallow hard and frequently, or to make forcible expiratory efforts with the mouth shut and the nose held. Pain may also be felt in the other bony cavities of the skull, such as the frontal sinus and maxillary antrum. Such symptoms are most likely to occur in workers suffering from acute or chronic catarrh.

The inability to equalize the pressure in the interior of the cavities is known to compressed air workers as "blocking," or being "blocked." Persons who are subject to chronic catarrhs are poorly adapted to compressed air work, as the swollen mucous membranes prevent free access of air to these cavities. Compression may give rise to intolerable pain, and there may be hemorrhages from the nose and ears because of the cupping effect.

As the air-pressure rises there is usually a sensation of warmth due to the fact that air when compressed becomes hot. Therefore, if the air is not properly cooled as it enters the air-lock, the temperature may rise considerably.

There is very little effect upon the pulse and the respiration, except that the respirations are slightly diminished in number. There is practically no effect upon the blood-pressure or the circulation.

Many observers have noted that caisson workers become thin and anemic, and some have explained this fact on the theory that the air-pressure drives the blood out of the skin and mucous membranes to deeper parts of the body. While it seems probable that the number of red blood-cells does become slightly diminished as a result of work

under compressed air, the pallor and loss of weight is in all likelihood principally due to another cause. The temperature of the interior of caissons is likely to be high, because of the heat given off in the compression of the air. Moreover, the conditions are usually such, because of excavations in watery soil, that the air of caissons is saturated with moisture. Besides this, compressing the air itself increases its relative humidity. Thus air 50 per cent. saturated with vapor will be 100 per cent. saturated if compressed to an additional atmosphere; and air 33 per cent. saturated will be 100 per cent. saturated if compressed to two additional atmospheres. Workers are therefore frequently exposed to high heat combined with a high degree of humidity. This is likely to be followed by the loss of appetite and weight and the characteristic pallor common to all who work under similar conditions.

As the pressure increases, the voice is said to take on a peculiar nasal quality. The inability to whistle as the pressure reaches two or more atmospheres has been noted by many writers. This is due to the fact that, owing to the greater density of the air, more force is required to produce vibrations. This inability to impress vibrations on the air also gives rise to sensations of slight numbness about the lips. In compressed air the sense of smell is also said to lose something of its keenness. This is not due to any loss of the sensitivity of the nose, but to the fact that owing to the greater density of the atmosphere, more resistance is offered to the escape of particles from odorous substances.

Many workers express a feeling of greater lightness and ability to perform muscular feats while under pressure, complaining of lassitude and fatigue on decompression. It is thought that these sensations are subjective, and not due to any quality resident in compressed air. Former writers have ascribed these sensations to stimulation of metabolism because of the increased tension of the oxygen in the air. Experiments, however, have shown that the presence of an increased amount of oxygen has no practical effect upon the rate of metabolism.

While the oxygen in chemical combination with the hemoglobin of the blood shows no material increase, there is naturally an increase in the amount of oxygen in simple solution in the blood-serum, sufficient to keep the blood in the veins from becoming dark. Venous blood in persons subjected to increased barometric pressure is, therefore, bright red, similar to the arterial blood.

Owing to the diminution in volume of gases in the intestines (which, of course, are at atmospheric pressure at the beginning of compression), a slight lessening of the abdominal circumference is noted during compression, so that the belt may be drawn up to an additional hole.

When once the air in the bony cavities of the body (middle ear, sinuses of the skull) has become equalized to the caisson pressure, the worker is entirely unconscious of the compression. Respiration and muscular movements are just as free as at atmospheric pressure. Hill states that when he and Greenwood were compressed in an experimental chamber to 92 lbs. excess pressure, a degree of pressure far in excess

of that to which caisson workers have ever been subjected and only occasionally supported by divers, there were no subjective symptoms whatever due to the great increase in barometric pressure.

ACCIDENTS WHILE UNDER COMPRESSION.—Caisson workers in general and divers in particular are naturally subject to certain peculiar accidents which are the direct outcome of the increased air pressure to which they are subjected. Thus, in caissons, in the event of sudden failure in the air-pressure, due to bursting of the air supply pipe, the water may rise suddenly in the caisson and drown the workers before they have a chance to escape. Again, caissons have exploded, causing fatalities. In tunnelling work, where the tunnel is driven in loose silt, "blow outs" have been known to occur, the compressed air escaping under the front edge of the shield up through the river bed in such quantities that the air-pressure cannot be maintained. Unfortunate workers have been caught in the rush of air and blown out through the river bed.*

Divers are subjected to serious accidents. If the air supply fails, or the air hose bursts, air may suddenly be driven out of the suit, and suffocation or a dangerous or fatal "squeeze" from the outside water pressure may occur.

"Squeezes."—"Squeezes" are among the accidents to which divers are subjected, and in all diving operations great care must be used to avoid them. In general a "squeeze" is caused by any substantial excess of the water pressure over the air pressure, and may be brought about in various ways. Consider, for instance, what would be the result if a diver were suddenly to fall a distance of from 20 to 30 feet, either into an unexpected hole in the bottom, or down the hatchway of a submerged ship, and his air supply were not increased proportionately to the rapidity of his fall. The diving-suit, as previously described, consists of an incompressible copper helmet and breast-plate, and a collapsible rubber suit. A fall of 30 feet will add an excess pressure of 15 lbs. to every square inch of the body. If, therefore, there were no increased pressure to the air supply to counterbalance this suddenly applied pressure from the outside, the air would be driven from the collapsible suit into the helmet. If the difference in pressure occasioned by the fall were not greater than could be counterbalanced by the compression of the air in the helmet due to the added volume driven in from the suit, no serious harm would result. If, however, this equality were not produced, the outside pressure would tend to drive the diver into his helmet, thus possibly producing severe or fatal injury. A fall of 20 feet, when the diver is working in comparatively shallow water, will produce more serious effects than when he is working at greater depths, for the resulting increase in pressure will be proportionately much greater when compared to the original pressure

* This is said to have occurred, without causing injury, to a worker in the course of the construction of the original Hudson River tube.

370 MORBID CONDITIONS DUE TO BAROMETRIC PRESSURE

in shallower than in deeper levels. Thus, a fall from 33 to 55 feet would have the effect of raising the excess pressure in the proportion of 15 to 25. A similar fall, from 165 to 187 feet, would increase the pressure only as 75 to 85. In the first instance, the diver would be subjected to pressure nearly 1.66 times greater than the original pressure; in the second instance, the pressure is only 1.13 times greater.

*Asphyxia.**—Asphyxia is a result of insufficient air or of failure of the air supply.

Accidental Blowing Up.—Through sudden increase in the air supply, or failure of the outlet valve to work, the suit becomes filled with air, the diver becomes lighter than the water, and tends to rise rapidly to the surface. This may cause harm in several ways. If the diver is blown up from a considerable depth, serious compressed air illness may result, or he may be injured by colliding with floating bodies.

Fouling.—The lifeline may become entangled in submarine obstructions, and thus prevent the diver from ascending. In this way, exposure to a high atmospheric pressure may be prolonged beyond the limits of safety. The situation usually requires that another diver descend and clear the diver who is fouled.

Mechanical Injuries from External Violence.—These are of many kinds and may happen in various ways.

Exhaustion.—Deaths from exhaustion in diving have occurred. It is probable that an inadequate air supply has been a factor in some instances.

Drowning.—French states that there are 2 cases of drowning on record. In both instances the helmet became detached. There is no danger of drowning because of a rent in the suit. So long as the air-pressure is maintained in the helmet, water cannot enter it. If the escape valve is closed completely,† air will enter the suit and force down the water, the excess escaping through the rent.

Oxygen-poisoning.—In the course of his investigations, Paul Bert found that when animals were exposed to a very high atmospheric pressure or to a lower pressure of pure oxygen, the high tension of the oxygen acted as a poison on the animal. It was thrown into spasms, and became stiff (like a piece of wood, as Bert described it), so that it could be lifted by a hind leg. These effects were observed whenever the tension of the oxygen was 2 or 3 atmospheres.

In addition to this, J. Lorrain Smith has shown that high pressures of oxygen, even though insufficient to produce convulsions, acted in a strongly irritant manner on the lungs, producing congestion and pneumonia. He found that exposure to an oxygen tension of 40 per cent. of an atmosphere for eight days had no effect; 80 per cent. of an atmosphere killed 2 mice in four days, which after death showed con-

* The following description of the accidents to which the divers are subjected is based upon statements made by French.

† With some kinds of diving apparatus, the valve cannot be completely closed.

gestion of the lungs, while 2 mice survived unharmed. An average oxygen pressure of $1\frac{1}{4}$ atmospheres killed mice in an average of sixty-four hours, 1.8 atmospheres in twenty-four hours, and 3 atmospheres of oxygen produced inflammation of the lungs in five hours. His results were confirmed by Hill.

These oxygen pressures, however, are never attained in caisson practice as, with compressed air, it would require 4 atmospheres excess pressure for the oxygen tension to be equal to 1 atmosphere, or 15 lbs. Moreover, exposure for some time is necessary before symptoms are produced. While, in deep-sea diving, divers may undoubtedly be exposed to a tension of oxygen which might exert a poisonous effect, or cause severe lung irritation if exposure were unduly prolonged, care is taken under such conditions to make the exposure short.

Bornstein reports that in a fire which took place during the construction of tunnels under the River Elbe, it was necessary to use smoke-helmets, in which the wearers breathed pure oxygen, in order to effect rescue work. As the excess pressure in the tunnels at the time was 2 atmospheres, it is evident that the wearers of the smoke-helmets breathed oxygen having an absolute pressure of 3 atmospheres. Pulmonary irritation was not observed in those who were exposed to this high oxygen tension for thirty minutes. Bornstein, however, justly concludes that this is due to the short exposure, and that this time should not be exceeded.

In the salvaging operations of the submarine F-4, a diver, W. F. L., became entangled and remained for a total time of three hours and forty-five minutes below the surface, at an average depth of 250 feet. The high partial pressure of oxygen to which this diver was subjected resulted in bronchopneumonia, which, according to French, was some time in clearing up.

Description of Compressed Air Illness.—It was not long after compressed air began to be used in construction work and diving before it began to be noticed that exposure to increased air-pressure brought with it a train of symptoms, which varied greatly in severity, from itching of the skin and slight pains in the bones and joints, to severe symptoms, such as heart-failure accompanied by paralysis of the extremities resulting often in permanent invalidism, or rapidly causing death.

HISTORICAL STATEMENT.—In his report on the sinking of the first coal-shaft by the use of compressed air, in 1839, at Châlons, Triger makes no mention of the occurrence of any symptoms among the workers. The first account of symptoms arising in workers, due to compressed air, was given by Pol and Wattelle, the cases coming under their observation during the sinking of a coal-shaft at Douchy in 1841. Pol and Wattelle were the first to make the striking observation that the symptoms coming on after exposure to compressed air made their appearance only after the subject had been decompressed. They coined the phrase, which has attained much currency among those who have investigated

compressed air illness, namely, "on ne paie qu'en sortant" (one only pays on going out). In sinking this shaft, a pressure of $3\frac{1}{4}$ atmospheres, gauge, was reached. The period spent in locking-in was usually fifteen minutes, and in locking-out, thirty minutes. There were numerous cases of illness. Out of 64 workers, 30 remained more or less well during the entire time employed, 23 were discharged because of severe symptoms, and 2 died.

The types of symptoms reported by Pol and Wattelle may be summed up as follows: difficult respiration; acceleration and hardening of the pulse; muscular pains, often very severe; cerebral symptoms; hebetude; loss of consciousness; deafness and blindness, very often permanent; and sudden death.

The following important conclusions were drawn by Pol and Wattelle from their observations: The compression of air up to $4\frac{1}{2}$ atmospheres is not of itself to be feared; it is readily borne, and infinitely better borne than a rarefaction of the air which is much less marked. It is the return to normal pressure which must be feared; this often brings about severe symptoms and may cause sudden death. After exposure to compressed air, the severity of the symptoms observed is proportionate to the pressure originally borne. Young persons support decompression from increased pressure much better than those of middle age. Observations show that the unfortunate effects of decompression are in direct proportion to its rapidity. *There is reason to hope that the most certain and most prompt way of alleviating symptoms would be immediate recompression.*

These opinions of Pol and Wattelle, based upon clinical observations, are entirely correct. Hill remarks that it is strange that these important conclusions should have been neglected by subsequent writers.

Following Pol and Wattelle, LeRoy de Méricourt published the first report concerning the illness of sponge divers. He mentions the frequent occurrence of paralysis and recommends that not less than one minute for every meter of depth should be spent in coming up to the surface, and that each diver should not spend more than two hours and thirty minutes per diem under water.

Since that time numerous authors have written of the symptoms following exposure to compressed air, notably in the case of the construction of the Caffr-Assyat bridge on the Nile, Babington and Cuthbert's studies of the symptoms observed among workers in the building of the Londonderry bridge, in October 1861, and the account of the symptoms observed among workers in the construction of the Mississippi bridge in 1869, at St. Louis. In the construction of this bridge, caissons were driven to the unprecedented depth of 33 meters, or 110 feet, requiring an excess pressure of 3.45 atmospheres. The construction of this work was marked by numerous and severe cases of caisson disease. Out of 352 workers, 30 had severe symptoms, of whom 12 died. During this work, the time of decompression was very short—only three or four minutes for locking-out. As the number and

severity of the cases increased, however, the time of the working shifts was very materially reduced, so that toward the end of the construction, the men only worked for one hour in compressed air. An account of the clinical observations made in this work is given by Jaminet, the surgeon employed by the company.

SYMPTOMS OF COMPRESSED AIR ILLNESS.—The most recent extensive report on work in compressed air is that of Keays, who describes the symptoms noted in the workers employed in constructing the Hudson River tubes. This work consists of 4 great tunnel systems, built by the use of compressed air, underneath the East and North rivers. Between March, 1906, and July, 1908, 4 tunnels, each 23 feet in diameter, were driven under the East River, from the foot of E. 33d Street in Manhattan to East Avenue, on the Long Island side. The distance was 6,176 feet. These tunnels are justly regarded as the greatest undertaking ever carried out up to that time by the use of compressed air. About 1,000 men per diem were kept at work in the tunnels, while the work was in active progress. Three thousand, six hundred and ninety-two cases of illness occurred among 10,000 men (36.92 per cent.), and there were 20 deaths (.2 per cent.). These men were medically examined and passed for this work. On the basis of man shifts (557,000), the percentage of illness was .66 per cent., of deaths .0035 per cent.

Keays makes the following classification of symptoms observed:

1. Cases showing pain in various parts of the body ("bends"), 3,278, or 88.78 per cent.
2. Cases showing pain, with local manifestations, 9, or .26 per cent.
3. Cases showing pain, with prostration, 47, or 1.26 per cent.
4. Cases showing symptoms referable to the central nervous system:
 - (a) Brain (hemiplegia, or paralysis of one side of the body), 4, or .11 per cent.
 - (b) Spinal cord:
 - (i) Disturbances of sensation, 36
 - (ii) Disturbances of movement, 34
 - (iii) Combination of sensory and motor disturbances, 10

Total number of cases, 80 or 2.16 percent.

5. Cases showing vertigo (staggers) 197, or 5.33 per cent.
6. Cases showing difficult breathing and a sense of tightness in the chest (chokes) 60, or 1.62 per cent.
7. Cases showing partial or complete unconsciousness, with collapse, 17, or .46 per cent.
8. Fatal cases:

with symptoms belonging to group 3,	6,
" " " " "	4, 5,
" " " " "	7, 9,

Total, 20 cases, or .54 per cent.

From this analysis we are able to judge the wide range of symptoms which may be comprehended under the general title of caisson disease or compressed air illness. In order to give the reader a clear idea of the symptoms arising from exposure to compressed air, the following description of cases is given, typical of symptoms belonging to each of the groups described by Keays.

Cases Showing Pain in Various Parts of Body.—Pains in various parts of the body are known among caisson workers as "bends." After decompression from 2 atmospheres or more excess pressure, fleeting pains in various parts of the body are probably more or less experienced by all caisson workers. The pains are most frequent in the legs, in the neighborhood of the joints. From his observations made during the construction of the tunnel under the River Elbe in Germany, Bornstein gives the following statistics as to the frequency of the location of the pains. In 615 cases of "bends," pains were observed in the lower extremities three hundred and seventy-two times, in the upper extremities one hundred and three times, and in both the lower and upper extremities, one hundred and forty times. One peculiarity of the pains is that they occur in the neighborhood of the joints. In the legs, they are usually felt about the knee-joint, and in the arms, about the elbow or shoulder-joint. The pains may be slight and fleeting, or most severe and lasting several days. The pains may be so excruciating as to cause sweating and pallor, and to cause the patient to writhe and cry out with pain. Occasionally local symptoms, such as swelling and collections of air under the skin, may accompany "bends."

Cases Showing Pain, with Local Manifestations.—Pain is more or less general and may be present in the abdomen. Pallor and sweating are present, the patient complains of weakness and dizziness, and may vomit. Keays noted mottling of the body in 13 cases, varying from blotching to bleeding under the skin, the discoloration varying in size from small spots to areas as large as the palm of the hand. In such cases loss of consciousness occasionally takes place.

Cases Showing Pain with Prostration.—In addition to the excruciating local pains, prostration and collapse may be present. The following is a summary of symptoms observed in cases reported by Keays:

1. In 2 cases, there was a semiconscious condition, with marked prostration, cured by recompression.
2. In one instance the man was unconscious and apparently dying, with mottling of the body. Following recompression, the general condition improved, but the man was still very weak. He recovered four days later.
3. One man, while drinking in a saloon, suddenly became unconscious. He regained consciousness when recompressed, but complained of extreme weakness. He recovered two days later, except for weakness in the right arm.
4. One patient was brought to the medical lock unconscious,

breathing noisily. He became conscious upon compression. His condition was good; he went home after a few hours' rest.

5. The patient was semiconscious, with marked prostration and mottling of the abdomen. He became conscious and could walk on recompression, but complained of pain in extremities. He recovered at the end of compression.
6. The patient was semiconscious, with marked prostration, difficult breathing, stomach symptoms and mottling of the trunk. He developed heart-murmur. He was improved by 2 compressions but still remained weak. He went home in twenty-four hours. Later he had sharp pains in his left side, and spit blood for several days. He was well at the end of two weeks.

The following case is given somewhat more at length because it shows the efficiency of recompression in an apparently desperate situation. The patient, twenty-six years old, worked for several months under compression. After working from 7 to 10 a.m. and from 1 to 4 p.m., under 34 lbs. gauge pressure, he went home. Forty-five minutes later he began to have general pain and sickness. When Keays arrived, the man was crying out in pain, was pale, bluish, and sweating. The pulse was rapid and weak. Before the ambulance arrived, the patient became unconscious, with noisy breathing and almost imperceptible pulse. When moved from the bed to the stretcher, he stopped breathing, and for what seemed to be a minute or more he seemed to be dying. After he had received a hypodermic injection of strychnin respirations began again. He was transferred as rapidly as possible to the medical lock, and recompression began, thirty minutes after the onset of symptoms. Massage was given. For some time there was no improvement, but about forty-five minutes later his color was better, and his pulse could be felt. About half an hour later, consciousness was regained, and questions were answered. He could sit up, but felt very weak. He continued to improve during slow decompression. Mottling was marked at one time, but became fainter. Upon the completion of decompression, four hours and thirty minutes later, the patient was wholly conscious, and could sit up with difficulty. The color was good, there was no sweating, the pulse was still rapid and weak, heart and lungs were apparently normal, the abdomen was tender, but not rigid nor distended, mottling was faint, and there was no paralysis. He was discharged from the hospital, cured, four days later.

Keays states that abdominal pain is justly feared by the caisson workers. It was a prominent symptom in many of the severest cases. He states: "With simple abdominal pain, one can never feel sure that a serious case is not threatened."

Mottling of the skin is also a sign of gravity. Itching of the skin, "sand-hog's itch," is a very common symptom on decompression. Hill has ascribed it to small air-bubbles in the subcutaneous fat. Erdman, however, believes that the bubbles are in the sweat-glands, rather than

in the fatty tissues, as this itching sensation is quite as common among the leaner as among the plumper workers.

Cases with Symptoms Involving the Nervous System.—Keays reports 4 cases in which symptoms point to embolism by gas-bubbles of the cranial blood-vessels:

1. The first case showed partial loss of power in the left arm and leg. This was relieved by recompression.
2. The next case was one of almost complete paralysis of the right leg and partial paralysis of the right arm, with increased reflexes. It was cured by recompression.
3. One case showed loss of power in the left arm and leg, and was cured by recompression.
4. After working for eight hours at 15 lbs. gauge pressure, this patient was decompressed in two or three minutes. Soon afterward, the right arm and leg became paralyzed, and he could not speak. He was cured by recompression.

Cases Involving the Spinal Cord.—Thirty-six cases showed disturbances in sensation, 9 had numbness or prickling sensation in one leg, 27 had numbness or prickling in both legs, and 17 of these had abdominal pain.

Thirty-four cases showed motor difficulties, classified as follows:

1. One patient had pain in the legs and abdomen, with partial loss of power in the left leg, only relieved by recompression. He recovered in two weeks.
2. Eleven patients had partial loss of power of both legs.
3. One patient had abdominal pain, also cured by recompression.
4. One patient had partial paralysis of one leg, and complete paralysis of the other. He was cured by recompression.
5. One patient had pain in the abdomen and limbs, partial paralysis of both legs, prostration, blotches on the chest and abdomen. He recovered on the third day.
6. Four patients had partial loss of power in both legs, with retention of urine. One of these patients, two years later, still walked stiffly and unsteadily, and was obliged to use a catheter.
7. Seven patients had complete loss of power in both legs, and were cured by recompression.
8. One patient had complete paralysis of both legs, with retention of urine. He finally regained the use of his legs, so that he could walk with difficulty.
9. One case was that of a "green hand" who was given a trial compression at 33 lbs. for one hour. He was decompressed in sixteen minutes. Paralysis of both legs followed fifteen minutes later. He improved under recompression and could walk. After this, the paralysis returned, with loss of control over the bladder and bowels. Eighteen months later he could walk, but with a spastic gait.

10. One patient had partial paralysis of both legs, with loss of control over the bladder and rectum. He was in the hospital for two weeks, but died later from some unknown cause.

11. In 5 cases, paralysis of both legs occurred, and there was no improvement on recompression. One resulted in death.

Cases Involving Combined Sensation and Movement.—Keays summarizes these cases as follows:

1. In 3 cases there was numbness combined with partial loss of power of both legs. This was cured by recompression.

2. There was one case of numbness and partial loss of power in both legs. The symptoms came back the next day in one leg, and were unrelieved by further recompression.

3. One patient had numbness and loss of power in one leg, complete loss of sensation and of power in the other. He was cured by recompression.

4. In one case there was loss of power in one leg, which was relieved by recompression. Later the patient complained of a dead feeling in both legs, and pain in the abdomen. The symptoms were cured by second recompression.

5. Two patients had complete loss of sensation and power in both legs, cured by recompression.

Cases Showing Vertigo.—Keays reports 113 cases with vertigo only, 42 with vertigo and vomiting, 29 with vertigo and pain in the limbs, 4 with vertigo and abdominal pain, 6 with vertigo and difficult respiration, one with vertigo, pain in the chest, and numbness in one leg, 2 with vertigo, prostration, and mottling.

Snell was the first to call attention to vertigo as a result of compression, in connection with the construction of the Blackwell tunnel.

Cases Showing Difficult Breathing ("Chokes").—This condition resembles a severe attack of asthma. Keays states that many, but not all, cases observed by him occurred when blasting was going on.

Cases Showing Partial or Complete Unconsciousness and Collapse.—The following case, reported by French in connection with the salvaging operations on submarine F-4, illustrates this type of compressed air illness. It was on the occasion of these salvaging operations that the maximum depth ever obtained by divers was reached. The depth of water in this instance was from 288 to 306 feet. Divers descended with all possible speed, and remained only the shortest practicable time at the bottom.

In this instance, the diver, W. F. L., entered the water at 10:39 a.m., and reached the bottom at 11:12. He spent fifteen minutes at 90 feet, adjusting apparatus, etc. On commencing to ascend, at 11:24 (12 minutes' stay on the bottom), he found himself foul at 250 feet. He went down again to clear himself, but was unsuccessful. He began

to ascend again at 11:35 a.m., and remained at a depth of 250 feet. Diver C. was then sent down. L. was cleared and brought up to 100 feet, at 2:25 p.m., the time under water up to this point being three hours and forty-six minutes. Instead of remaining at 100 feet to undergo decompression, L., in spite of telephone instructions to the contrary, climbed up the ladder of his own accord, to a depth of 60 feet, which he reached twenty minutes later. Twenty minutes later, having reached 40 feet, he collapsed, and failed to answer the telephone. He was brought to the surface at once, his diving suit being cut from him. At that time he was conscious, and able to talk, but collapsed a moment later. He was placed at once in a recompression chamber, and the pressure raised to 75 lbs. The patient was unconscious, cyanotic, not breathing, his pulse was imperceptible. Respiration started as the pressure was applied in the recompression chamber. When the pressure reached 75 lbs. the patient suddenly recovered. At 3:14 he was breathing, sitting up, and rational. The pressure was then gradually reduced in the recompression chamber, until 20 lbs. was reached, when he suffered from severe pains in the joints, followed soon afterward by abdominal pains and vomiting. The pressure was increased, and the vomiting left him, the only symptoms remaining being the joint pains, which were exceedingly severe, causing him to kick and scream. Pressure was then slowly reduced, whereupon the patient was removed from the chamber and taken to the sick bay. There were no symptoms showing involvement of the nervous centers. The patient complained bitterly of joint pains. Large areas of subcutaneous hemorrhages appeared over the chest and abdomen. The body was cold and the pulse not palpable at the wrist. Pain was so severe as to require morphin for its relief. The patient gradually improved, though suffering from bronchopneumonia because of the exposure to the high oxygen pressure.

Fatal Cases.—There were 20 fatal cases noted by Keays during the Hudson River tunnel work. In the great majority of these cases, symptoms came on in from fifteen to thirty minutes after decompression. In one instance they came on immediately after decompression; in one instance ten minutes after decompression; in one instance one hour after decompression; in one instance one and a half hours after decompression; and in one instance two hours after decompression.

The general symptoms were pains, often abdominal, with sickness, followed by sudden unconsciousness and collapse. Death followed.

In 4 cases death followed in one hour or less; in 3 cases in five hours or less; in 6 cases in twenty-four hours or less; and in 7 cases death was more or less delayed—from fifty hours to one hundred and forty-four days.

From the foregoing account of the symptoms, it is plain that compressed air illness is a protean malady which may attack the victim in many ways. It is indeed a striking and dramatic affection, coming on as it does without warning when the victim is in the full tide of his powers and feels perfectly well.

CAUSE OF COMPRESSED AIR ILLNESS.—Early Speculations.—As has been mentioned before, it is decompression from a high to normal atmospheric pressure which gives rise to the symptoms of compressed air illness. Until the course of events which produce these symptoms was first suggested by Hoppe, in 1854, and conclusively demonstrated by the brilliant and convincing experiments of Paul Bert, from 1872 to 1878, the cause of the symptoms furnished a fertile field for speculations, all based upon misconceptions of the operation of physical laws, of the kind in which medical literature too frequently abounds, even at the present day.

All the erroneous theories that were advanced were based upon the hypothesis that the excess pressure to which the body was subjected caused, in some way, mechanical injury to the organism. The authors of these mechanical theories could not get away from the idea that the body was supporting a tremendous load when subjected to increased air-pressure.

Thus Brizé-Fradin, in his quaint treatise on "*La Chimie Pneumatique Appliquée aux Travaux sous les Eaux*" (Pneumatic chemistry applied to submarine work), thought that the diver escaped the effects of the increased pressure through some mysterious action of the "vital forces," which modifies "general laws and places in the class of demonstrated truths that, which, at first sight, would appear difficult of explanation."

Again, Pol and Wattelle, in spite of their correct conclusions, could not overlook the mechanical cause of compressed air illness. This, they conceived, was due to venous congestion caused mechanically by the pressure driving the blood into the organs. They explained the fact that the symptoms appeared only after decompression by calling attention to the circumstances that, while under pressure, venous blood is bright red, instead of dark, owing to the excess oxygen dissolved therein. This highly oxygenated state of the venous blood prevented the occurrence of symptoms while the patient was under pressure. When return to ordinary atmospheric pressure took place, however, the excess oxygen was lost from the venous blood, while the congestion still remained; hence symptoms ensued.

Guérard was the first to point out that increased amounts of nitrogen, as well as of oxygen, would be dissolved in the body fluids, but he too was disturbed by the "frightful" load upon the body surface caused by exposure to increased pressures amounting to some 100 tons at five atmospheres. He believed that the loss of flesh observed in compressed air workers was due to increased internal combustion from the excess of oxygen present, and that the pains in the extremities were of a rheumatic nature and due to the chilling following decompression.

In this country, Jaminet, in writing on the causes of compressed air illness as observed in the course of the construction of the Mississippi River bridge, at St. Louis, in 1871, believed that the symptoms of compressed air illness were produced, with but a very few exceptions, by

the exhaustion of the system under certain circumstances. According to Jaminet, the cooling which takes place as the air-pressure falls in the locking-out process produces chilling of the body, which leads to the symptoms.

Babington and Cuthbert, in their report on the cases of illness observed by them during the construction of the Londonderry bridge, suggested that, because the brain and spinal cord were inclosed in a bony case, they could not follow the changes in atmospheric pressure as quickly as the other more elastic parts.

Bouchard is responsible for the conception that, as the gases in the intestines become compressed, pressure is exerted upon the abdominal wall. As this resists the displacement, it acts like a large cupping glass and sucks the blood into the interior of the organs.

MacNaughton advanced the belief that compressed air illness was, in some way, due to "frictional electricity" accumulated by the air in its passage through the compressing pumps and delivery pipes.

Again, A. H. Smith, in the United States, in his treatise on "Physiologic, Pathologic, and Therapeutic Effects of Compressed Air," supports the congestive theory, believing that the symptoms are produced because the blood has been forced into the cranium and spinal canal with a pressure of 30 or 40 lbs. to the square inch, but that it continues to circulate because the entire system is subject to this pressure. Smith supposes that the vasomotor mechanism becomes entirely suspended and that the blood-vessels are as passive "as the water-pipes in a house."

True Cause of Compressed Air Illness.—The above are merely examples of the riot of speculation as to the causation of compressed air illness, due to ignoring the operation of physical laws. Little reflection is required to detect their absurdity. It seems indeed remarkable that the fact was lost sight of that the tissues of the body, consisting as they do of a large percentage of water, are, like water, practically incompressible, and instantly transmit pressure in all directions, so that if the pressure on the exterior of the body is equalized by the respiration air at similar pressure, no damage from the pressure can result. Were this not the case, the force exerted by the normal atmospheric pressure would be quite sufficient to render life impossible. The fact (pointed out by Regnard) that the abysses of the sea are teeming with life at depths at which the weight of the column of water is equivalent to a pressure of some 200 atmospheres, or 3,000 lbs. to the square inch, evidently escaped the notice of these theorists.

We now know that symptoms of compressed air illness are brought about, on return to normal pressure, by the liberation of bubbles of gas dissolved under excess pressure in various parts of the body.

We have seen, by the operation of Dalton's law, that the fluids and tissues of the body take up gas in proportion to the partial pressure of these gases in the atmosphere. It is evident that if these gases are absorbed at a given tension and if the individual is subsequently exposed to an atmosphere in which the tension of these gases is very much

reduced, the excess of the gases dissolved in the tissues will be given off until their tension is equal to the diminished tension of the new barometric pressure.

If the change from a higher to a lower barometric pressure is made gradually, no harm will result, as the escape of the gases will be gradual also. If, however, the pressure is too rapidly diminished, the difference in tension between the tissue gases and that of the atmosphere becomes so great that the gases dissolved in the tissues of the body are suddenly liberated, with resulting bubble formation.

We have here a fact which perfectly explains not only the symptoms of caisson disease, but their diversity. As different parts of the body saturate and desaturate at varying rates, the tension of the gases may be higher in some parts of the body than in others at any given moment during decompression. This determines the location of bubble formation. If, for instance, the gas-bubbles are liberated in the neighborhood of joints, severe pain is the result, which may be due partly to the plugging by bubbles of the blood supply of the nerves supplying those joints, and partly to the mechanical pressure of the bubbles. If the gases are liberated so suddenly as to fill the capillaries of the lungs full of air-bubbles, the pulmonary circulation becomes at once greatly impeded, if not impossible, and sudden death with respiratory symptoms and cardiac failure or severe collapse may follow. In a similar fashion, the sudden liberation of bubbles in areas of the brain and spinal cord is an effective cause of the form of compressed air illness known as "diver's paralysis" or of cases showing symptoms of involvement of the brain, such as vertigo, apoplectiform seizures, or paralyzes of various kinds.

The bubbles consist practically only of nitrogen gas. While excess oxygen is also dissolved in the blood-plasma, this gas plays no part in the causation of caisson disease, for the reason that the tissues readily absorb any excess oxygen and the amount dissolved in the blood by the excess pressure is seldom but a small proportion of the amount which exists in the blood in chemical combination. It would, however, be quite possible to produce the symptoms of compressed air illness by oxygen alone, were an individual exposed to a high pressure of pure oxygen and suddenly decompressed. In addition to this he would also undoubtedly suffer from the symptoms of oxygen-poisoning already mentioned.

Demonstrations of Truth of Theory as to Cause of Compressed Air Illness.—The first suggestion that caisson disease was due to liberation of gases in the blood came from F. Hoppe, who in 1851 experimented on the effects of sudden decompression. Unlike the case of workers in compressed air, Hoppe produced decompression by rapidly exhausting the air from receivers in which small animals were placed. He found that if the pressure was very abruptly reduced, air-bubbles were found in the heart and large venous trunks. Hoppe found that on reduction of the barometric pressure from 760 mm. to 30 mm. the animal suddenly

fell down unconscious, but revived on restoration of the pressure. From this occurrence he concluded that the illness of workers in compressed air was due to the sudden release of gas-bubbles in the blood and tissues, and suggested that an effective way of relieving the symptoms would be immediate recompression.

Hoppe, however, was not the first to suggest recompression as a suitable treatment for symptoms of compressed air illness, as this is clearly stated as one of the conclusions in the work of Pol and Wattelle, to which reference has previously been made. In the works of several other authors, such as Panum and Leroy de Méricourt, one may find the suggestion that the symptoms of compressed air illness are due to the sudden liberation of gases in the blood during decompression.

It remained, however, for Paul Bert, by his magnificent series of investigations, which are reported in full in his work "*La Pression Barométrique*," published in 1878, to demonstrate that compressed air illness was due not to compression but to decompression, and that the symptoms were generated by the liberation of gas-bubbles in various parts of the body. Those who have subsequently investigated compressed air illness owe a heavy debt to Bert for his fundamental researches.

Bert exposed animals to high pressures and then decompressed them in two or three minutes. Gas was found in all the small veins.

A dog was compressed to 8 atmospheres gauge, and decompressed in one minute, forty-five seconds. On leaving the compression chamber, he ran around the room, felt happy, and wagged his tail. In three or four minutes, he cried lamentably, and endeavored to bite his hind legs, which were becoming paralyzed. Upon auscultation over the heart gurgling sounds were heard on the right side, but nothing on the left. Two or three minutes later his cries ceased; paralysis was complete, as to both movement and sensibility. Respiration became difficult, the heart slowed and the animal died in twenty-five minutes after decompression. Gas-bubbles were found generally throughout the venous system, in the portal vein, but not in the arteries. Innumerable little bubbles were seen in the fatty tissue under the muscles and thorax, in the subaponeurotic fat, along the back, in the omentum, the mediastinum, the grooves of the heart, and the fatty tissue in the spinal canal.

In another instance, a dog was placed in the compression chamber, and subjected to a pressure of 10 atmospheres. The glass windows in the compression chamber suddenly burst during Bert's absence from the laboratory. This produced a violent explosion, and, of course, immediate decompression. The animal apparently died instantly, although previous observation through the window had shown that prior to the explosion it was perfectly well. The animal was so blown up that it had become cylindrical, and great difficulty was experienced in withdrawing it through the door of the chamber. There was emphysema (bubbles of air) underneath the skin, in and beneath the muscles. When the abdomen was opened, the gas which distended it escaped with a whistle. The right heart was full of gas, as well as all the

veins, the pulmonary arteries and the pulmonary vein. There was no air, however, in the left auricle, nor in the aorta. Gas was found in the anterior chamber of the eye, and in the spinal fluid. The nerve fibers of the spinal cord were dissociated by bubbles of gas, which were not in the vessels. No hemorrhages were found either in the brain or the spinal cord. The lungs were a little congested, but no blood was in the windpipe. Fifty cubic centimeters of gas, drawn from the right side of the heart (there was much more gas in the heart than this), had the following composition upon analysis: oxygen 1.9 per cent., carbon dioxid, 15.1 per cent., nitrogen, 83 per cent.

The above are examples of very numerous experiments made by Bert, all of which confirmed his thesis that symptoms of compressed air illness are caused by improperly managed and too rapid decompression, and are due to the liberation of bubbles of gas (chiefly nitrogen) in various parts of the body. He next showed how, by so managing the rate of decompression as to allow the gradual disengagement of excess gas dissolved in the blood and tissues, all dangerous symptoms could be avoided.

Bert concludes as follows: "To sum up, improperly managed decompression beginning from several atmospheres causes symptoms of variable gravity, according to compression, the rapidity of decompression, species of animal, the individual, and the actual state of the individual during the experiment.

"These symptoms must be attributed to the disengagement of the nitrogen which has been stored in excess in the organism, according to the dicta of Dalton's law.

"This gas passes into a free state in the blood-vessels and the different organic fluids, in the very texture of the tissues; it may thus, according to circumstances, stop the pulmonary circulation, render bloodless and cause the softening of certain regions of the nervous system, and particularly the lumbar enlargement of the spinal cord, lacerate the tissues, produce swellings, and a more or less extensive emphysema. The severity of the symptoms depends both upon the seat and extent of these multiple disorders.

"A gradual decompression of 12 minutes to the atmosphere is necessary to protect dogs from symptoms, when the compression has been raised to the neighborhood of 10 atmospheres.

"Either an immediate recompression or recompression subsequent to the respiration of oxygen in cases where gurgling is heard in the heart is the only method of combating efficiently decompression symptoms."

All persons who read Bert's work will be struck at once by the simplicity and directness of his experimental methods, the judicial frame of mind in which he attacks the problem, the convincing conclusions drawn from his experiments, and the lucidity with which they are discussed. It is indeed strange that this work of Bert's was not immediately accepted.

The first criticism which was brought against its validity by those

who still clung to mechanical theories in spite of their absurdity on physical grounds, was that the pressures employed by Bert in his experiments (7 to 10 atmospheres) are higher by far than those to which any caisson workers are subjected, and, up to that time, had never been encountered even by divers. It did not occur to the objectors, as has been shown by subsequent investigators, that the size of the animals subjected to increased pressure, and hence the rapidity of the circulation, play a most important part in the rate at which the individual saturates and hence subsequently desaturates. In the case of a very small animal, such as a mouse or a bird, in which Hill estimates the heart beats at the rate of 500 to 600 a minute, and a complete round of the circulation occurs in a second or two, it is evident that such animals will saturate and desaturate at an extremely rapid rate. Excess gases with which the tissues are charged after decompression are, therefore, removed with rapidity from the body, so that no time is given for bubble formation, unless extremely high pressures are used. The animals which were the subject of Bert's experiments were chiefly dogs of moderate size. In many instances Bert does not give the weight of the animal used, but the average weight of 10 dogs in experiments in which weights were given was 7.52 kilograms, or about 16½ lbs. Such animals would have a circulation more rapid by far than a human being. It is evident, however, that, although it was necessary to modify the conditions of the experiment in order to suit the species experimented upon, the facts demonstrated by Bert are fundamental in nature, are based upon the operation of physical laws which are invariable, and must apply both to men and to the lower animals.

Subsequent workers have done no more than to amplify and extend Bert's observations, and to work out their practical application to compressed air work. Among these workers may be mentioned Blanchard; Regnard, who, after careful examination of the spinal cords of animals which had been rapidly decompressed, brought forth new confirmation for Bert's theory; Cassaet, who studied the question as to whether, as Bert believed, the gases were actually free in the blood in the form of bubbles; Catsaris, who published careful and thorough studies of the illness of the Greek sponge divers; and Phillipon, who experimented on compressing animals in an atmosphere of oxygen and nitrous oxid. This gas possesses a far greater solubility in the body fluids than nitrogen. When animals were decompressed suddenly after exposure to high pressure, this gas produced some rather extraordinary effects in the way of swelling and collection of gas-bubbles in the blood and tissues.

The construction of the locks of the Nüssdorf works in Germany on the River Elbe gave the opportunity to Heller, Mager, and Von Schroetter to make most careful studies of compressed air illness, which were greatly amplified by experimental work on the lower animals. Their monumental treatise on compressed air illness, which appeared in 1900, is a mine of information for those who wish to study such affections. Many of the facts here set forth have been derived from this work.

Heller, Mager, and Von Schroetter repeated in a general way Bert's work, and were able to confirm his results. They showed, as did Bert, that gases were set free in the blood after rapid decompression, and that the principal gas was nitrogen. They also established on a surer basis the hypothesis that in man these effects may be brought about by decompression from lower pressures than in the case of the smaller lower animals.

Although little room was left for doubt in the case of those who carefully read the works of the experimenters referred to, to clinch the proof of the causation of compressed air illness, further evidence has been brought forward by Leonard Hill, and his co-workers, J. J. R. McLeod, C. E. Ham, and Major Greenwood, in the following brilliant experiments:

1. They inclosed a frog's heart in a small chamber with thick glass windows, and showed that it continued to beat in a normal manner even when the pressure was raised to 50 atmospheres. They also showed that a frog's muscle could be stimulated to contract in normal fashion under like conditions.

2. In caterpillars, air is conveyed directly to the body-cells by the finely branching passages or tracheæ. Their circulating fluid carries no oxygen to the tissues as does the blood. Sudden decompression from 27 atmospheres had no ill results on these worms unless they had eaten leaves while exposed to the pressure. Then they would burst, due to the swelling of the swallowed air.

3. They inclosed a dog or cat (which had previously been made insensible by anesthetics) in a pressure chamber, and connected a large artery to an apparatus that would record the blood-pressure, the entire apparatus and animal being inside the pressure chamber. No change was brought about either in the blood-pressure or in the pulse-beat by raising or lowering the pressure in the chamber to 2 or 3 atmospheres.

4. They designed a chamber with thick glass windows, in which was placed a frog, so arranged that the web of a foot could be illuminated by a powerful arc lamp, and the image thrown by means of a microscope on a screen. The magnification was sufficiently great to allow the capillaries to become visible and the circulation of the frog to be seen. They found that no changes in the circulation (thus visibly demonstrated on the screen) were caused by quickly raising or lowering the pressure by 20 atmospheres. On decompression from long exposure to high pressure, however, they had the satisfaction of seeing bubbles begin to appear in the capillaries, as demonstrated in the manner just described, grow in size as the pressure was diminished, and finally stop the circulation, and again when the pressure was raised, diminish in size and finally disappear.

5. Again Hill and McLeod placed anesthetized dogs in a pressure chamber, having first connected an artery to a tap, so that samples of blood could be drawn off in a vacuum pump for analysis. They were

able to confirm Bert's observations and show that nitrogen dissolves in the blood in proportion to the partial pressure to which the organism is exposed, approximately 1 per cent. of nitrogen being dissolved in each atmosphere of pressure.

6. Hill and Ham further killed rats by rapid decompression from 10 atmospheres, chopped up the bodies under water, and collected the gas set free from the bodies under a funnel full of water. Upon analysis they found that from 80 to 90 per cent. of the gas was nitrogen, and the rest chiefly carbon dioxid, with a trace of oxygen.

7. They killed mammals by rapid decompression, and upon opening the right side of the heart under water, analyzed the gas obtained. They showed that from 80 to 90 per cent. was nitrogen, the rest being carbon dioxid with only a trace of oxygen. The carbonic acid gas escapes from the blood because the nitrogen set free acts as a vacuum in relation to the carbon dioxid. The oxygen unites chemically with the blood, and is used up by it, and therefore only a trace is found. (This confirms the results of Von Schroetter.)

Hill and Greenwood showed that after animals are killed by sudden decompression from a pressure of 7 to 8 atmospheres, gas-bubbles are set free in the fat of tissue-cells, such as in the liver and kidneys, which actually burst and destroy the structure of the tissue-cells. Hill states that the liver and kidneys may appear foamy with bubbles in such cases. The fat, also, in all cases of rapid decompression, is honey-combed with bubbles, like the beaten white of an egg. Air-cells in the lungs may be burst and the lobules of the lungs distended by the force of the expansion of air in them. The blood-vessels are found to be filled with columns of bubbles.

Factors Predisposing to Compressed Air Illness.—In the multitude of observations which have been made on the occurrence of compressed air illness, both in men and animals, certain facts stand forth prominently.

(1) *Question of Relative Immunity.*—From the very nature of the circumstances causing compressed air illness, *i. e.*, the liberation of bubbles of gas in some part of the body, there can be no such thing as immunity from compressed air illness, yet it has been observed that while many become victims of this affection, under precisely similar circumstances, others escape, or individuals escape symptoms during weeks and months of work only to be severely affected under what are apparently precisely similar conditions.

Generally speaking, however, we can predict on the basis of physical inspection of the worker whether or not he is likely to have severe symptoms. There seem to be three factors which preëminently influence predisposition to the disease. These are *age, degree of fatness, and size.*

As early as 1854, in their report, Pol and Wattelle called attention

to the fact that the young, between eighteen and twenty-six, were relatively immune from severe symptoms, which affected mainly those of later youth and early middle age. Of the 25 men who were discharged because of serious illness, 19 were over forty, 5 between thirty and forty, and 1 between twenty-eight and thirty.

Hill and Greenwood have analyzed the occurrence of symptoms of compressed air illness from the record given by Snell, of observations in the Blackwell tunnel works. Snell gave the following table (Table 1) showing the age distribution of the men medically examined by him, the number of men taken ill whose ages were recorded, the proportion of illness to every hundred men passed (cited after the table of Hill).

TABLE 1. RELATION OF AGE TO COMPRESSED AIR ILLNESS (SNELL).

Age	No. of Men Examined and Passed.	No. of Men Taken Ill Whose Ages are Recorded.	Proportion of Illness to Every 100 Men Passed.
15-20	55
20-25	145	15	10.3
25-30	152	37	24.3
30-35	91	19	20.9
35-40	61	14	22.9
40-45	38	10	26.3
45-50	3	5	166.0
	<hr/> 545	<hr/> 100	

This table as it stands does not give us the necessary information as to the actual sick rate in relation to the age, for the reason that at the Blackwell tunnel works medical inspection was not compulsory at first. This table has been subjected to the following analysis by Hill and Greenwood:*

Supposing that the men examined by Snell were a fair sample of the workers, their ages may be used as a measure for the age distribution of the entire body of workers engaged in that enterprise. If, now, there were no special liability to compressed air illness on account of age, the number of men at any given age who would suffer would be $\frac{n'}{N}$ of the total number of cases (100), N representing the total number of men whose ages are recorded (in this instance 545) and n' the number of men in each particular age group. By performing these calculations Hill and Greenwood derived the results shown in Table 2, which shows the theoretical number of cases for each age group if there were no special liability to compressed air illness on account of age.

* Hill, L. E. "Caisson Sickness." London, 1909, page 165.

Comparing the figures in the last columns of both tables, it will be seen that decompression symptoms had a decidedly higher predilection for individuals of higher age groups.

This special predilection may be due to either or both of the following factors: (1) an increased amount of fat with advancing years, (2) diminished activity of the circulation.

The attention of the reader has already been called to Vernon's discovery that nitrogen is about six times as soluble in fat as in the other tissues of the body. With advancing years there is a tendency to accumulate fat, so that the effective weight of the blood in proportion to that of the rest of the body is diminished. Thus in a very spare wiry individual the effective ratio of the blood to body weight may be not greater than 1/20 of the body weight, whereas, in a fat individual, the actual weight of the blood may be no more than 1/30 of the body weight, and, because of the high absorption coefficient of fat for nitrogen, its effective weight may not be more than 1/40 of that of the body.

TABLE 2. THEORETICAL RELATION OF AGE TO COMPRESSED AIR ILLNESS (Hill and Greenwood on basis of Snell's table).

Age.	Actual Number Affected.	Theoretical Number Affected.
15-20	0	10.09
20-25	15	26.61
25-30	37	27.89
30-35	19	16.70
35-40	14	11.19
40-45	10	6.97
45-50	5	0.55

In addition to this, the circulation becomes less active with advancing years. According to the author's own observations, distinct hardening of the brachial artery is often found even before the thirtieth year in those who follow laborious occupations. We can therefore see that, with advancing years, not only does the amount of fat in the body increase, but the wear and tear on the vascular system has been such as distinctly to diminish the ease and rapidity of the circulation.

To render the worker relatively immune to caisson disease, therefore, two physical attributes seem to be required, (1) good circulation, (2) absence of much bodily fat.

The ideal caisson worker would be a young, rather wiry man, with firm, hard muscles, and active movements. It is easy to see how such physical attributes serve to protect their possessor from the onset of symptoms. Because of the lean, firm structure of the body tissues, there is but little fat to dissolve large quantities of excess nitrogen. Desaturation of the different parts of the body will therefore proceed at a much more nearly uniform rate, there being less lag in the process. Furthermore, because of the rapid circulation and high effective weight of the blood as compared to the total weight of the body, saturation, it is true, will take place at a greater rate, but so will desaturation.

In addition to the age and bodily fatness, we may also speak of mere body weight itself as having an influence upon susceptibility to compressed air illness, large individuals being more susceptible than small. This arises from the following physical conditions: Saturation and desaturation are effected by means of a surface (the walls of the air-cells in the lungs). Inasmuch as surfaces are to each other as the squares, and solids as the cubes, of their respective dimensions, it is evident that in small individuals the surface of the lungs will be greater in proportion to the bulk of the body than in large individuals of similar proportions. Therefore saturation and desaturation will proceed at a faster rate in small persons than in large.

This is well brought out in the experimental work which has been done on compressed air illness. Thus the evidence that mice can stand rapid decompression better than rats is reasonably strong, and in general, throughout all the lists of experiments made by numerous investigators, small animals usually stood without harm sudden decompression from pressures which would infallibly kill large animals, such as men.

(2) *Diet.*—It seems probable that the diet of the worker may play some part in his susceptibility to symptoms on decompression. When the diet consists of an abundance of fatty substances, the chyle as it flows from the intestines, and the contents of the lacteals, will contain fat in abundance. This would naturally increase the capacity for absorption of nitrogen, owing to the high solubility of nitrogen in fats. On *a priori* grounds, the best diet for caisson workers would be one consisting more especially of proteins and carbohydrates, with a restricted consumption of fats. Those engaged in compressed air work, especially at high pressures, should indulge sparingly in fried foods, pork, bacon, and the like.

(3) *Influence of Alcohol.*—The multiplied experience of many observers shows that alcoholics have increased susceptibility to caisson disease. There are several reasons for this: (1) In chronic alcoholics the circulation is likely to be impaired, thus retarding desaturation of the slow parts of the body; (2) many alcoholics suffer from an increase of fat in the liver, which serves as a store house for excess nitrogen; (3) there is a tendency toward the accumulation of superfluous fats in other parts of the bodies of alcoholics, especially of beer drinkers; (4) it is well known that in heat spells in our large cities, alcoholics are peculiarly liable to heat strokes and heat exhaustion. The hot, humid conditions under which caisson work is often necessarily conducted places the alcoholic under a physiological strain, which he can only meet with difficulty, and at the expense of his circulatory system. For this reason, the circulation is likely to suffer, desaturation be effected with corresponding slowness, and symptoms develop, when those of temperate habits would escape.

(4) *Effects of Local Chilling and Constrained Posture.*—Whenever, by reason of his work, it is necessary for a compressed air worker to

maintain a relatively immobile condition, or when an extremity is immersed in cold water, local symptoms, such as bends, are apt to arise on decompression. Bornstein observes that, in many instances in which workers who had hitherto escaped suffered from bends in an extremity, it was usually found that the affected limb had either been subjected to a prolonged soaking, or that the necessities of the work had caused the subject to assume a strained posture in which the limb was more or less immobile. Such conditions have the effect of slowing the circulation in the affected part. As a shift usually lasts long enough to effect a high degree of saturation, this slowing of the circulation causes slow desaturation in the affected part of the body, and hence favors the occurrence of local symptoms.

So far as divers are concerned, local chilling may be a factor of some importance in the onset of symptoms. The wrist-bands of the diving-suit constrict the wrists and may lead to considerable retardation of the circulation in the hand. The water in which the diver works is often very cold, so that on long exposures to moderate depths the diver may become thoroughly chilled before coming to the surface. Such chilling retards the circulation in outlying portions of the body, and symptoms may make their appearance after exposures to pressures which under more favorable conditions would have produced no unpleasant results.

(5) *Factors in the Working Environment.*—Most caissons are hot and humid places to work in. Air while being compressed becomes greatly heated, and the relative humidity is increased in proportion to the increased pressure.* The following table shows the rise in temperature for each increase in pressure:

<i>Pressure Above Atmospheric. Pounds</i>	<i>Temperature of Air. (F.) Degrees</i>
0	60.0
14.7	175.8
29.4	255.1
44.1	317.4
58.8	369.4
73.5	414.5
88.2	454.3
102.9	490.6
117.6	523.7
132.3	554.0
205.8	681.0
379.3	781.0

These figures relate to dry air. Moisture in the air will increase

* Air 40 per cent. saturated at 1 atmosphere will be 80 per cent. saturated at 2 atmospheres, where the temperature is kept constant.

these figures, because the specific heat and conductivity of air is raised by moisture.

When the heated compressed air strikes the watery soil in the caisson, the cooling effect may cause precipitation of the moisture in the form of mist. Hill observed such a mist in the Blackwell tunnel, in the course of his visit there in 1911.

Such hot and humid atmospheres have the effect, (1) of diminishing the ability of the workers to work, (2) of interfering markedly with the escape of heat from the body. It is well known that physical exertion raises the temperature of the body, and that the body's excess heat must escape; otherwise death, with symptoms of heat stroke, will rapidly ensue. Researches by Rübner, by Flügge, and his co-workers, by Haldane, and by Hill, have shown that the important thermometer measurement, so far as bodily comfort is concerned, is the reading of the wet bulb thermometer. Haldane showed that physical work without dangerous rise in the temperature of the body is an impossibility after the wet bulb thermometer exceeds 84° F. (28.8° C.). This arises from the fact that as soon as we encounter wet bulb temperatures in excess of 74° F. (23.3° C.) the only way in which excess heat can escape from the body is by the evaporation of moisture from its surface. The wet bulb temperature of caissons must very often be close to the limit named by Haldane. It should also be borne in mind that wet bulb temperatures in excess of 74° F. produce extreme discomfort, and exhaustion when severe physical toil is attempted, even though the resting subject may be fairly comfortable. As the work required of the "sand hog" is often hard, he must rely on the evaporation of sweat from his body to maintain his bodily temperature within safe limits. We have seen that the compression of air raises the percentage of relative humidity. Moreover, the very density of the air itself renders evaporation more difficult. The absence of through drafts in caissons renders the air more or less stagnant.

It is no wonder that under such circumstances caisson workers at the end of the shift are bathed in sweat, the pulse is small and frequent, and a sensation of great exhaustion is present. All such conditions must have a marked influence in diminishing the volume of the circulation and hence the rate of desaturation.

During the construction of the Forth bridge, Hunter noted that the most dangerous times, so far as the onset of symptoms was concerned, were (1) when soft wet silt was being removed, and (2) when concrete was being laid. Hill suggests that the excessive sick rate observed under these conditions was due to the increased moisture in the air.

Measures should be taken to prevent the wet bulb thermometer from rising too high in the interior of caissons, and for cooling and drying the air. Hill suggests that the air might be led over tubes of calcium chlorid, a relatively cheap material, which would rapidly absorb the moisture out of the air. The calcium chlorid could then be dried and used again. Electric fans to stir up the air would also greatly assist the evaporation of sweat from the body.

PREVENTION OF COMPRESSED AIR ILLNESS.—Because of the imperfect understanding in the past of the causation of compressed air illness, large numbers of lives have been sacrificed, and still larger numbers of individuals rendered hopeless invalids.

In a list of fatalities in compressed air work, compiled by Heller, Mager, and Von Schroetter, in 1900 there is a list of 97 fatal cases.

While it seems improbable that minor cases of "bends" under high air pressure can be totally eliminated, still it should be possible, by paying due attention to the following principles, to prevent the occurrence of cases of serious illness and death:

1. Careful selection of the personnel.
2. Proper management of decompression.
3. Proper medical supervision of the personnel.
4. Provision for rapid recompression in case of illness.
5. General hygienic precautions with respect to the work itself.

Careful Selection of the Personnel.—Careful medical examination of compressed air workers before assigning them to duty is a prerequisite. The physical attributes which best fit a man to withstand decompression after exposure to high air pressure should be borne in mind. As previously stated, the ideal "sand hog" is a young, lean, wiry individual, free from functional or organic diseases of the lungs and circulatory system. In general, a man of forty-five years of age or more should not be employed. Age, however, is a relative rather than an absolute disqualification. A small wiry man forty-five years of age, presenting no signs of hardening of the arteries, with low blood-pressure, would probably be a better subject than a stout young man of indolent disposition.

As a general rule, the following classes of persons should not be allowed to work in compressed air.

1. Very stout persons.
2. Persons having organic disease of the heart.
3. Persons having organic disease of the kidneys.
4. Persons having respiratory disease, tuberculosis, chronic bronchitis, emphysema of the lungs.
5. Persons showing general disease of the vascular system, such as arteriosclerosis.
6. Persons suffering from chronic catarrh of the nose and middle ear.

Standards of size and fatness must however be regarded as relative. For instance, a person who might be considered somewhat too stout for compressed air work might still have such an active circulation as to enable him to desaturate safely.

The reasons for rejecting persons suffering from organic disease of

the lungs, heart, or kidneys are evident. Owing to the effects of these diseases on the circulation, we may expect persons suffering from them to become greatly exhausted by the work.

Management of Decompression.—The proper management of decompression is the fundamental means of avoiding serious cases of compressed air illness. So far as compression or locking in is concerned, the only precaution which it is necessary to observe is that the passages of communication between the middle ear and the outside air, and also those leading to various cells in the bones of the skull, are free, so that any air in the interior of these cavities quickly acquires the new pressure. As previously remarked, these passages are opened up by frequent swallowing or by shutting the mouth, holding the nose firmly with the fingers, and making strong expiratory efforts.

Persons habituated to compressed air can take high pressures with great rapidity. Thus in the diving and salvaging operation of the F. 4, diver F. C. descended 306 feet in nine minutes, subjecting himself to an excess pressure of nearly 10 atmospheres, or 150 lbs. to the square inch. In the experimental diving performed in connection with the work of the Admiralty Committee on Deep Diving, Mr. Catto descended 180 feet (6 atmospheres excess pressure) in 1 minute 30 seconds and Lt. Damant in 1 minute 40 seconds.

There is no need, therefore, for the subjection of workers to a gradually increasing pressure, as was advocated by former writers who took a mechanical view of the symptoms brought about by exposure to increased barometric pressure.

The time and method of decompression, however, are of great importance. It is by attention to the management of this all-important period that the toll of suffering and death exacted by compressed air work may be minimized.

(1) *Supersaturation of Body Tissues and Fluids.*—Were it not for the fact that the body tissues are susceptible to a considerable degree of supersaturation with gases before bubbles are given off, symptoms due to bubble formation on decompression would be far more easily produced. Furthermore, the albuminous nature of the body fluids and their greater viscosity, as compared with water, for instance, discourages the formation of bubbles.

After a careful consideration of all the fatal cases which have been recorded, Haldane found that it was doubtful whether any serious symptoms would ever occur unless the excess pressure exceeded 1.25 atmospheres. At pressures above 1.25 atmospheres, mild cases of compressed air illness began to be recorded, their frequency and severity increasing rapidly with higher pressures unless the time of exposure were shortened or the time of decompression increased. The lowest pressure at which Haldane found records of fatal cases of compressed air illness was 23 lbs., or 1.6 atmospheres of excess pressure. From this Haldane concludes that the blood and tissues of the body will stand supersaturation to $1\frac{1}{4}$ atmospheres excess pressure without involving the risk of bubble formation.

This conclusion of Haldane enables us to outline the theoretical principles along which decompression should proceed.

It is evident that what is required is, first, to produce as rapid desaturation as possible, and, second, so to manage desaturation that the difference in pressure between the body gases and those of the outside air shall never become dangerous, i. e., ever exceed the ratio of 2 to 1. It is evident that there should be as great a difference as is safe between the tension of the tissues in the body, and those of the air breathed, in order to assist the rapid diffusion of gases brought by the blood from the tissues to the lungs. On the other hand, this pressure difference must not become too great, otherwise bubble formation will take place.

No particular precautions are required in decompression from excess pressure not exceeding $18\frac{1}{2}$ lbs. to the square inch, as supersaturation of the body tissues and fluids will prevent bubble formation. It is with the higher pressures, therefore, that we concern ourselves in the following discussion.

(2) *Methods of Decompression.*—Two principal methods of decompression have been advocated: first, gradual decompression, and second, the stage method of decompression.

(a) *Gradual Decompression.*—In the gradual method of decompression, the pressure is slowly and uniformly reduced, at a predetermined rate, until atmospheric pressure is reached. In stage decompression, the pressure is abruptly reduced by stages to various levels, a pause being made after each successive reduction, until atmospheric pressure is reached.

In the past, in most of the principal engineering works constructed by compressed air, the uniform method of decompression has been used. Great variations in the period of decompression have been observed. Naturally, in default of knowledge as to the causation of compressed air illness and the relation between the pressure to which the person has been subjected and the severity of the symptoms, the tendency has been to hasten the period of decompression. Air-locks are likely to be small and greatly crowded at the end of shifts. The workers are wet with perspiration from labor in hot and humid caissons. As the pressure is lowered in the lock, the air becomes chilled, and its moisture often precipitated as mist, because of the sudden lowering of its temperature. Just beyond the door of the air-lock lies the prospect of food, warmth, dryness, rest, and recreation. It is no wonder then, that in the absence of rigid regulations, air-valves are surreptitiously opened to let the pressure out as rapidly as possible. The following have been the times of decompression in some of the well-known works:

TABLE 3. TIMES OF DECOMPOSITION IN SOME WELL-KNOWN CAISSON WORKS.*

Date	Place	Maximal Pressure (Gauge)	Period of Decompression
1839	Douchy mines, shaft-sinking.....	2.5 atm.	30 min.
1862	Bayonne, bridge over Adour.....	3.5 atm.	12 min.
1883	Cubzac bridge.....	7.6 atm.	3.18 min.
1885	Bridge over Eider.....	2.6 atm.	2 min. 5.30 sec.
1889	Wyoming	40.42 lbs.	10 min.
1895	Nussdorf Works, Danube.....	2.5 atm.	35 min.
1905	Westelijke Viaduct, Amsterdam.....	2 atm.	32½ min.

Gradual decompression is the method which is prescribed in the Dutch law regulating work in compressed air, in the French regulations, and in the laws of New York and New Jersey.

Paul Bert came to the conclusion, as the result of his experiments on dogs, that a decompression period of twelve minutes to the atmosphere was sufficient to avert dangerous symptoms in these animals.

Gradual decompression is the method which has been advocated by Heller, Mager, and Von Schroetter, as the result of their observations in connection with the construction of the locks on the Danube, at Vienna, which furnished them the clinical material for their work on compressed air illness. In order to be safe, according to Von Schroetter, at least two minutes should be used in reducing the pressure 1/10 atmosphere, or for each 1½ lbs. This would cause the following decompression periods:

20 minutes from 15 lbs.
27 " " 20 "
33 " " 25 "
40 " " 30 "
50 " " 35 "
58 " " 40 "

Decompression at this rate, especially from high pressure, has not been successful in preventing severe symptoms, and even death. This method of gradual decompression has been subjected to the following analysis by Haldane:

"In order to avoid the risk of bubbles being formed on decompression, it has hitherto been recommended that decompression should be slow and at as nearly a uniform rate throughout as possible. We must therefore carefully consider the process of desaturation of the body during slow and uniform decompression. For convenience in calculation, we may imagine the process as occurring in a series of time-intervals, the first half of each of which is spent at the pressure existing at the beginning of the interval, and the second half at the pressure

* Prepared from table given by Hill.

existing at the end. Let us suppose, for instance, that the body has been completely saturated with nitrogen at an excess pressure of five atmospheres of air, and that decompression occurs at a rate of one atmosphere in twenty minutes. The process may be divided into five periods of twenty minutes, during each of which the pressure falls one atmosphere. We can then easily calculate how far desaturation will have gone at the end of each period, and from these data construct a desaturation curve.

"Let us first consider the mean desaturation rate of the whole body, assuming that, when the pressure is suddenly raised or diminished to a certain level, the tissues will on an average saturate or desaturate themselves by 50 per cent. in twenty-three minutes, which was shown above to be a probable average rate. A reference to the curve (Chart

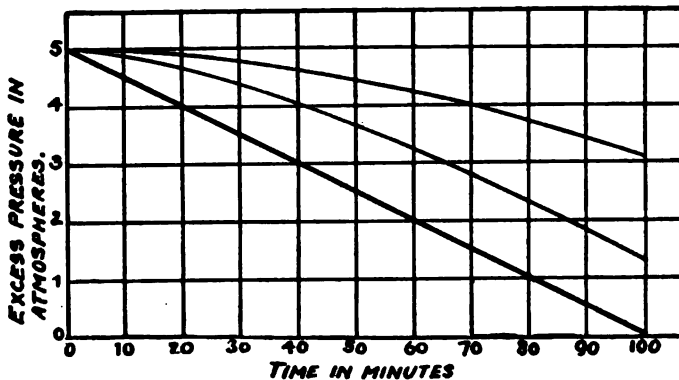


CHART 2 (according to Haldane).—SHOWING THE LAG IN DESATURATION OF QUICKLY AND SLOWLY SATURATING PARTS OF THE BODY WITH UNIFORM DECOMPRESSION.

1, on p. 365) shows that ten minutes' exposure to the reduced pressure of four atmospheres in excess will reduce the saturation by twenty-eight per cent. of the difference between five and four atmospheres, *i. e.*, by 0.28 of an atmosphere. Hence at the end of twenty minutes the tissues will, on an average, be saturated to 4.72 atmospheres. Ten more minutes at 4 atmospheres will reduce the saturation to 4.5 atmospheres, and ten minutes at three atmospheres will further reduce it by twenty-eight per cent. of 4.5—3, *i. e.*, by 0.42 atmosphere. Hence at the end of the second twenty minutes the saturation of the tissues will be at 4.08 atmospheres. Continuing this calculation, we get the desaturation curve shown in Chart 2, from which it will be seen that when atmospheric pressure is reached, the tissues are still saturated to an excess pressure corresponding to 1.4 atmospheres of air.

"Chart 1 also shows a similar curve for the parts which saturate and desaturate most slowly, and which, according to our previous calculations, take one and a quarter hours to become half saturated. At the end of decompression these slowly desaturating parts, as shown on the curve, are still saturated to 3.15 atmospheres. This of course represents a most formidable excess; and, as will be shown below (p. 401 of Haldane's book) uniform decompression at this rate is dangerous even to goats, and would certainly be dangerous to men, who desaturate a good deal more slowly than goats.

"Inspection of Chart 2 shows that with uniform decompression the nitrogen pressure in the body lags behind that of the air, and that (in the case of the slowly desaturating parts) the amount of the lag increases during the whole time of a decompression lasting 100 minutes. No other result seems possible, and actual experiments point strongly in the same direction, as will be shown presently. We must emphatically dissent from the conclusion drawn by Heller, Mager, and Von Schroetter that decompression at the uniform rate of twenty minutes an atmosphere prevents any dangerous retention of gas in the body. To prevent a maximum lag of more than one atmosphere, it would be necessary to decompress at a rate of over one and a half hours an atmosphere if the decompression were uniform and from an excess pressure of 5 atmospheres.*

"The examples given will be sufficient to illustrate the extreme slowness at which desaturation must occur with a uniform rate of decompression. This slowness has never hitherto been recognized, but must evidently be reckoned with in devising measures for the prevention of caisson disease."

This criticism of Haldane's on the dangerous lag in desaturation peculiar to slow decompression seems unanswerable. In justice to the recommendations of Heller, Mager, and Von Schroetter, however, it should be stated that, at the time of their studies, although they realized that, because of lack of uniformity in the distribution of the blood, some portions of the body would saturate and hence desaturate more slowly than others, the fact (discovered by Vernon) that nitrogen gas was approximately 6 times more soluble in fats, oils, and fat-like bodies (such as for instance lipoids of the nervous system) than in the other tissues, was unknown. Moreover, the total bulk of the blood compared to that of the body was assumed by Heller, Mager, and Von Schroetter to be greater than it really is.

The dangerous lag in desaturation shown by Haldane's analysis is more especially due to the excessive solubility of the excess nitrogen in the fats and oils. The excess pressure of 1.4 atmospheres (21 lbs.) remaining in the quickly saturated parts of the body, after gradual de-

*"It is evidently a mistake to assume that a given rate of uniform decompression, such as twenty minutes per atmosphere, is either necessary for safety in all cases, or would be actually safe except from some limit of pressure. From a pressure below this limit, the rate will be unnecessarily slow, and from above it dangerously fast."

compression from 5 atmospheres in one hundred minutes, as shown by Haldane's calculations, is not after all excessive and is probably within the supersaturation limits, without bubble formation, of the more quickly saturating parts of the body. It is the excess pressure of 3.4 atmospheres in the slowly saturating parts which, as Haldane puts it, constitutes a formidable excess. It is precisely in these slow parts, among which portions of the nervous system must be included, that bubble formation is likely to be followed by severe symptoms. These considerations led Haldane to work out his theory and practice of stage decompression.

(b) *Stage Decompression*.—As previously mentioned, Haldane, as the result of inquiry, found that injurious symptoms practically never occur on decompression, unless the excess pressure exceeds 1.6 atmospheres (2.6 atmospheres absolute, 23 lbs. gauge pressure, or a ratio of 2.6 to 1), although slight symptoms may occur as a result of rapid decompression from such a pressure. Inasmuch as the relative volumes of a gas at different pressures are as the ratio of these pressures to each other, it seems likely that it would be safe to decompress rapidly from any excess pressure to a lower pressure, provided the ratio of change in absolute pressure is not greater than the 2.6 to 1 just mentioned.

Experimental evidence seems to justify this belief. Thus a number of experiments made by Dr. Boycott and Lt. Damant, in a steel chamber at the Lister Institute, showed that a sudden drop from 75 lbs. excess pressure to 24 lbs. excess pressure in 200 experiments was without especial risk to goats. This observation has been further confirmed by Hill and Greenwood, so far as pigs are concerned. These authors state that pigs, in the shape of their bodies, structure of their organs, and their diet, resemble man far more closely than do goats. They are also bad subjects for exposure to compressed air because of their fatness. Hill concludes (*Caisson Sickness*, page 207) that, at any rate up to 5 or 6 atmospheres, the absolute pressure can always be reduced without risk to half the absolute pressure at which the tissues are saturated.

Haldane considers that, although the absolute pressure may be reduced by somewhat more than $\frac{1}{2}$, to be on the safe side in actual practice, the ratio of reduction should be as 2 to 1. By making this reduction the first step in decompression, Haldane states that the following advantages are obtained:

“The process of desaturation can therefore be hastened very greatly, by rapidly reducing the absolute pressure to $\frac{1}{2}$, and so arranging the rest of the decompression that the saturation in no part of the body shall ever be allowed to increase more than about double the air pressure. The main advantage of this plan is that the discharge of nitrogen from the tissues is from the outset of decompression increased to the greatest rate which is safe. The rate of discharge evidently depends on the difference in the partial pressure of nitrogen in the venous blood and in the alveolar

air; and by keeping this difference at the maximum consistent with safety, a great saving in time is effected."

Haldane has called this method stage decompression, and his general principles consist first in dropping the pressure rapidly until $\frac{1}{2}$ the absolute is reached, and, from this point on, decompressing slowly at a calculated rate until atmospheric pressure is reached.

The following is an illustration of the application of this method in a practical instance (quoted from an article by Boycott, Damant, and Haldane*) :

"It will be convenient to consider first the case of diving to a very great depth, and we shall take as an extreme example the case of exposure at a depth of $35\frac{1}{2}$ fathoms (213 feet) of sea-water, corresponding to an excess pressure of nearly 6.5 atmospheres, or an absolute pressure of 7.5 atmospheres.

"Let us first suppose that the body of a diver is completely saturated with the nitrogen of air at this pressure, and that it is required to conduct his ascent to surface as rapidly as possible but without any risk of symptoms due to bubble formation, *i. e.*, in such a way that, in accordance with the principles already laid down, the nitrogen pressure in no part of the body shall ever be more than double that of the air breathed at the same time.

"The first step would obviously be to reduce the absolute pressure to about half, *i. e.*, from 7.5 atmospheres absolute to 3.75 or from 6.5 atmospheres in excess to 2.72. This would be *ex hypothesi* the greatest initial drop in pressure which would be perfectly safe. The remainder of the decompression would evidently need to be conducted in such a way that the maximum partial pressure of nitrogen in any part of the body should diminish at double the rate of the fall in absolute pressure of the air. The ascent of a diver can be conveniently regulated from the surface by signalling to him to stop or come on at every ten feet as indicated on the pressure gauge attached to the pump. We may therefore divide the ascent into stages of ten feet, and the short periods occupied in the actual ascents may be neglected.

"Since the depth was 213 feet, corresponding to 246 feet of water in absolute pressure, it would be safe to come up at once to a depth corresponding to 123 feet of absolute water pressure, *i. e.*, to 90 feet of actual depth. Consequently the first stage would be a rapid ascent of 123 feet, and it would be necessary to wait here before the next ascent of 10 feet, until the maximum partial pressure of nitrogen in the body had fallen to that of the nitrogen in air at $2 \times (80 + 33) = 226$ feet of absolute water pressure. The difference between 246 and 226 is 20, and this is 16 per cent. of $213 - 90 = 123$, the difference between the original and the reduced pressure. The most slowly desaturating

* "Prevention of Compressed Air Illness." Cambridge Journal of Hygiene, 1908, viii, 359.

parts of the body will, according to our previous calculations, take 75 minutes to give off half of any excess of nitrogen which they may contain at any given air pressure; by inspection of the curve (Chart 2) it will be seen that they will take about nineteen minutes to lose 16 per cent. of the excess. Hence a delay of nineteen minutes would be necessary at 90 feet before coming up to 80 feet. At 80 feet the partial pressure in the body would require to fall an amount corresponding to 20 feet, which is about $17\frac{1}{2}$ per cent. of $193 - 80 = 113$, the new difference in relative pressure between the nitrogen in the body and in the air. This would necessitate a delay of twenty-one minutes before ascending to 70 feet. The further delays needed would be twenty-three minutes at 70 feet, twenty-six minutes at 60 feet, thirty minutes at 50 feet, thirty-five minutes at 40 feet, forty-two minutes at 30 feet, fifty-one minutes at 20 feet, and sixty-two minutes at 10 feet. It would thus take three hundred and nine minutes, or more than five hours, to reach surface."

This shows the very long time required to effect decompression safely by any method wherever the exposure has lasted a sufficient time to allow thorough saturation of the body tissues to occur.

The times necessary therefore for safe decompression from the higher pressures are so long as to be wholly impracticable, if the exposure is not reduced so that decompression is begun before full saturation of the tissues has taken place.

By adjusting the time of exposure to the pressure, Haldane has worked out a series of decompression times for divers by the stage method just described, which not only render work in great depths free from serious risks to life, but place the periods of decompression within practical limits.

It should be noted at this point that there is a fundamental difference between diving work and caisson work. The diver usually works for short periods under high pressures, whereas the caisson worker is exposed for much longer periods to more moderate pressures. We thus find that, when divers suffer from compressed air symptoms, these very rarely consist of joint pains, such as "bends," but are far more likely to be serious symptoms of paralysis and collapse. This is due to the fact that, in divers, the very slowly saturating parts such as bones and joints have had, owing to the shortness of the exposure, but little time to proceed far with saturation. Hence, the symptoms arise in the more quickly saturating parts of the body. The longer shift of caisson workers, however, gives opportunity for a greater degree of saturation in the slowly absorbing parts of the body.

(c) *Stage Decompression Applied to Caisson and Tunnel Work.*—The method of stage decompression advocated by Haldane and his co-workers for divers has been modified somewhat to meet the special case of caisson and tunnel workers, for whom we must provide decompression from exposures usually lasting not less than three hours to a shift, and not less than six hours each day. With such exposures, the first

step, as in the case of divers, is to reduce the initial absolute pressure to one-half. Calculation shows that further decompression by the stage method so closely approximates uniform gradual decompression that the remainder of the "locking out" may be conducted by uniform slow decompression.

The following illustrative example, quoted from Haldane and his colleagues, will serve as an illustration of this method of decompression, as applied to caisson and tunnel workers.*

Supposing the men were working at an excess pressure of 24 lbs. (an absolute pressure of $24 + 15 = 39$ lbs.) in three-hour spells, with an hour's interval for a meal, the first step on locking out, as in the case of divers, would be rapidly to reduce the absolute pressure to one-half $\frac{24 + 15}{2} = 19\frac{1}{2}$ lbs., or an excess pressure of $4\frac{1}{2}$ lbs.). After the first three-hour spell of work, the slow decompression would be at the rate of 1 lb. in three minutes, or $3 \times 4\frac{1}{2} = 13\frac{1}{2}$ minutes in all. After the second shift the rate would be 1 lb. in five minutes, corresponding to $22\frac{1}{2}$ minutes in all. If the men were to stay for the whole period in compressed air, the rate of slow decompression would be 1 lb. in seven minutes, corresponding to $31\frac{1}{2}$ minutes in all.

Table 4, worked out by Haldane and his colleagues, shows the rate of decompression by the stage method, in caisson and tunnel work.

TABLE 4. RATE OF DECOMPRESSION IN CAISSON AND TUNNEL WORK.
(Boycott, Damant and Haldane.)

Working pressure in lbs. per sq. inch.	Number of minutes for each pound of decompression after the first rapid stage.		
	After first three hours' exposure.	After second or third three hours' exposure, following an interval for a meal.	After six hours or more of continuous exposure.
18-20 lbs.	2	3	5
21-24 "	3	5	7
25-29 "	5	7	8
30-34 "	6	7	9
35-39 "	7	8	9
40-45 "	7	8	9

In actual practice the results by the stage method, so far as divers are concerned, have met the indications. By the stage method of decompression, divers were decompressed without serious symptoms in the salvaging operations of the F. 4, after being exposed to an excess pressure corresponding to 306 feet of water (nearly 10 atmospheres gauge

* BOYCOTT, DAMANT AND HALDANE: Prevention of Compressed Air Illness. Cambridge Journal of Hygiene, 1908, viii, 374 *et seq.*

VOL. VI.—26.

pressure). The only exception was one diver who became fouled, and remained three hours and forty-five minutes under the water, and who furthermore disregarded instructions in making his ascent. This diver certainly would have died had not means for immediate recompression been at hand.

In caisson and tunnel work, however, and in experiments on animals, decompression by the stage method has not given the results which might be hoped for. Bornstein, as the result of his observations at the Elbe tunnel works, where there was an excess pressure of 2 atmospheres, compared the effect of decompression by stage and by uniform method, with results given in Table 5.

From this table it would seem that there is a slight advantage on the side of the stage method, but by no means a decisive one.

Subsequently in the course of these works, the men were obliged to climb a steep staircase immediately upon leaving the air-lock. This exercise after decompression proved far more effective in reducing the number of cases of "bends" than decompression by the stage method.

Hill and Greenwood, using the stage method on pigs, obtained the following results:

Exposure at + 75 lbs. for 90 minutes.
Decompression to + 20 lbs. in 10 minutes.
Pause at + 20 lbs. for 85 minutes (average).
Decompression to + 0 lbs. in 18.3 minutes (average).

							<i>Per cent.</i>
Deaths	0	0
Dyspnea	0	0
Normal	12	100
						<hr/> 12	

Average weight of pigs, 55 lbs.

Exposure to + 75 lbs. for 120 minutes.

Decompression to + 20 lbs. in 10 minutes.

Pause at + 20 lbs. for 102 minutes (average).

Decompression to + 0 lbs. in 14.3 minutes (average).

Deaths	1	2.86	} 5.72
Dyspnea	1	2.86	
Normal	33	94.29	
						<hr/> 35		

Average weight of pigs, 73.85 lbs.

Similar decompression of fat pigs, weighing from 81 to 115 lbs., from + 90 lbs., allowing a pause of from one hundred and five to one hundred and twenty minutes at +20 lbs., gave unfavorable results, 7

deaths and 1 severe case of compressed air illness being noted among 27 pigs. Hill states, however, that it must be borne in mind that the pigs were very fat, and slept on the floor of the caisson during decompression (thus diminishing the rapidity of the circulation). The experimenters tried arousing the pigs by giving them electric shocks, but could not succeed in making them active.

On the other hand, using the method of uniform decompression, Hersent, at Bordeaux, in 1894, after animal experimentation, found 3 workers who were willing to subject themselves to exposure to high air pressures. The men were enclosed in a steel chamber, the experiments being conducted under the observation of a Commission composed of 5 members of the Bordeaux Faculty of Medicine.

In one experiment, the individual was subjected to an excess pressure of 4.8 kilograms to the square centimeter (68.27 lbs. to the square inch). Thirty-five minutes were consumed in reaching this pressure; the length of the exposure was one hour, and the time of decompression

TABLE 5. COMPARATIVE EFFECTS OF STAGE AND UNIFORM DECOMPRESSION.

Days.	Workers.	Cases of Illness.
20 stage	526	15
16 uniform	528	17
18 stage	529	12
16 uniform	529	14
14 stage	536	12

two hours and three minutes. The only symptom observed after decompression was a little itching.

In the second experiment, a pressure of 5 kilograms to the square centimeter (71.16 lbs. to the square inch) was reached after compression lasting one hundred and fifty minutes, with no unfavorable results except a little itching, as in the first experiment.

On the third trial, the same subject was compressed 5.4 kilograms to the square centimeter (76.81 lbs. to the square inch) in forty-five minutes, remained under the pressure one hour, and was decompressed in three hours and three minutes.

Hersent decompressed men with safety after one hour's exposure in:

26 minutes from 2.5 atmospheres
46 " " 3.0 "
60 " " 3.5 "
77 " " 4.0 "
100 " " 4.5 "
150 " " 5.0 "
183 " " 5.5 "

Hill points out that Hersent safely used a method which is theoretically the poorest, namely, from 5 to 4 atmospheres in forty-five

minutes, from 4 to 3 atmospheres in thirty-five minutes, from 3 to 2 atmospheres in thirty minutes, from 2 to 1 atmospheres in twenty minutes, and from 1 to 0 atmospheres in fifteen minutes, inasmuch as the decompression rate was slower at first and more rapid at the end.

Hill and Greenwood, in their experiments, successfully exposed themselves to high pressure; Hill to 75 lbs. once, and Greenwood to 92 lbs. once and 75 lbs. three times. During the experiment in which Greenwood reached the excess pressure of 92 lbs., fifty-four minutes were spent in reaching this pressure, whereupon the pressure was gradually reduced, two hours and seventeen minutes being required to reach atmospheric pressure. On leaving the chamber, Greenwood noticed some itching in both forearms, especially the right, which was followed by pains in both arms.

Hill and Greenwood came to the conclusion that it was an important matter during decompression to move and turn every muscle and joint of the body, so as to accelerate the circulation. They found such precautions sufficient to remove disagreeable symptoms.

It seems evident, then, that while, from a theoretical standpoint, stage decompression should be far superior to uniform decompression, in practice it is possible to decompress from high pressures with the uniform method with apparent safety.

In his paper delivered before the 15th International Congress on Hygiene and Demography, Japp, who was the Managing Engineer for S. Pierson and Son, the contractors on the four East River tunnels for the Pennsylvania Railroad, suggested that the times allowed for decompression by the stage method for pressures between 35 and 45 lbs. are too long for practical purposes, for, according to Haldane's figures, it would take ninety and one-half minutes to decompress from 40 lbs. pressure. Japp assumes that an excess pressure of 25 lbs. in the tissues would be safe at the close of decompression. He has therefore drawn up a table (Table 6) of procedure in which Haldane's theory of stage decompression is applied, but which permits the maximum excess pressure in the tissues to be 25 lbs. instead of 19 lbs. This has the effect of shortening the times materially.

In the course of the construction of the East River tunnels, Japp relates that it was necessary to raise the pressure in the tunnel to 40 lbs. gauge. This occurred after he had become acquainted with Haldane's theory of stage decompression. Fortunately it was possible to arrange to have the men exposed to this pressure pass through 3 sets of air-locks. The decompression was carried out in the following way: The men were ordered to take five minutes in the first lock, decompressing from 40 lbs. to 29 lbs.; then followed a walk of 1,000 feet in a section of the tunnel which was kept at a pressure of 29 lbs. This required about 10 minutes, including waiting to get into the second air-lock, and collecting stragglers. Eight minutes were spent in the second air-lock, where the pressure went from 29 to 12½

lbs., ($27\frac{1}{2}$ lbs. absolute) or one-half the original absolute pressure ($40 \text{ lbs.} + 15 \text{ lbs.}$)

$$\frac{2}{2} = 27\frac{1}{2} \text{ lbs.}$$

Another walk of 1,000 feet in the second tunnel section took place at this pressure, and when the third lock was entered, the pressure was reduced to atmospheric in fifteen minutes. Thus, forty-eight minutes in all were spent in decompressing from 40 lbs. excess pressure, by this method. Japp calculates that, in the course of such decompression, the maximum excess pressure of gas in the body tissues was 27 lbs. Thus the men did what was equivalent to emerging instantaneously from a pressure of 27 lbs. No severe or fatal cases resulted under these conditions. Three hundred and thirty men were employed for thirty-six days, working two shifts of three hours each, separated by a rest interval of three hours at atmospheric pressure. There were over 20,000 individual decompressions without a mishap. If the decompression

TABLE 6. DECOMPRESSION PROCEDURE, BASED UPON 25 LBS. MAXIMUM AIR SATURATION OF BODY ON EMERGING.

Gage pressure.	Reduce pressure in 3 minutes to:	Total time in air-lock after 8 hours' work.	Total time in air-lock after 3 hours' work.	Total time in air-lock after 2 hours' work.	Maximum air saturation of body on emerging.
Pounds	Pounds	Minutes	Minutes	Minutes	Pounds
27	6	9	25
30	$7\frac{1}{2}$	24	25
32	$8\frac{1}{2}$	33	25	..	25
35	10	..	35	..	25
40	$12\frac{1}{2}$..	48	..	25
42	$13\frac{1}{2}$..	51	37	25
45	15	42	25
50	$17\frac{1}{2}$	48	25

had been conducted according to the modified table submitted by Japp, the maximum gas in the tissues on emerging would have been 25 lbs. instead of 27.

On the other hand, it should be pointed out that while, in this instance, the theoretical maximum saturation of the tissues on emerging was 27 lbs., it was probably below this figure usually, for the reason that the men walked a distance of 2,000 feet, or very nearly half a mile, during the course of decompression.

Moreover, Japp informs us that all the men employed at this stage of the work were seasoned compressed air workers. The previous experience of these men implies that physically they possessed the attributes which make the individual well adapted to work at high barometric pressure, *i. e.*, they had good circulations and were not encumbered by superfluous fat.

Aids to Rapid Desaturation of the Body.—In addition to so managing decompression after exposure to high barometric pressure that at

no time shall there be a dangerous excess of gas stored in the tissues of the body, there are two ways in which we can help the body to get rid of the excess gas which it holds:

1. By increasing the rapidity of the circulation.
2. By breathing a gas (*i. e.*, oxygen) which of itself is harmless so far as storing in the tissues is concerned, but which will displace the excess of nitrogen.

If vigorous exercise is taken during the time of decompression, a greater number of rounds of the circulation will occur in the same period. Consequently the amount of nitrogen gas discharged will be greatly increased.

Bornstein has calculated that the same volume of nitrogen which would be eliminated by uniform decompression in one minute will be removed by stage decompression in from .5 to .6 minutes; by light bodily work in from .2 to .35 minutes; and by vigorous exercise in from .1 to .2 minutes. Reference has already been made to Bornstein's observation of the marked diminution in the number of cases of decompression illness seen in the course of the construction of the Elbe tunnels in Hamburg, due to exercise. Hill is of the opinion that if sufficiently vigorous exercise is taken, theoretically safe times of decompression could be shortened by at least half. In their own experiments, Greenwood and Hill found that moving all the muscles during decompression prevented unpleasant symptoms after exposure to very high excess pressures (75 lbs. and 92 lbs.). We have thus in exercise a potent means for averting serious consequences after exposure to high barometric pressure.

In air-locks, however, this means is not made use of as a rule. The locks are small and crowded, the men are more or less fatigued from the work of the previous shift, and the tendency is to remain as passive as possible, many men taking naps while the pressure is being reduced. Moreover, the chill caused by the loss of heat in the air as the pressure declines has a tendency to empty the skin of blood, contract the surface vessels, and increase the resistance to the circulation. Besides this, sleep itself retards the circulation. Thus Boycott and Damant found that dormice, weighing only 10 or 12 grams, could usually be killed, when hibernating, by decompressing them in five seconds from 75 lbs. pressure, whereas decompression in the same time from 120 lbs. had hardly any effect on them when they were in a lively condition.

It is evident that we can hasten the process of desaturation after exposure to excess pressure by causing the individual to breathe an atmosphere in which the partial pressure due to nitrogen is zero. This can be done by having him inhale oxygen gas. In this way the greatest possible difference in tension between the nitrogen in the tissues and that of the air breathed is created, the nitrogen being rapidly disen-

gaged. This will take place if an atmosphere of oxygen is breathed, at a tension corresponding to the tension of nitrogen in the tissues. It will, of course, take place with still greater rapidity if the tension of the oxygen is less than that of the nitrogen in the tissues. Unless the difference in tension between the oxygen breathed and that of the nitrogen in the tissues is too great (*i. e.*, greater than 2 to 1), no bubble formation can take place because the nitrogen as it leaves the tissues enters into solution in the blood. Because of the dangers of oxygen-poisoning this method would not be practicable if it were necessary to use tensions of oxygen in excess of 2 atmospheres. The observations of Bornstein show that, provided the period of inhalation is not more than thirty minutes, oxygen at a tension of 2 atmospheres will not produce symptoms.

In work at moderate pressures, the inhalation of oxygen might well be dispensed with, exercise being substituted, if necessary, as a means for assisting the process of desaturation. When, however, it is necessary to decompress from high pressures (35 lbs. and over for caisson workers) the risk of the onset of symptoms could be very materially reduced by commencing the inhalation of oxygen after the first rapid reduction in pressure (in decompression by the stage method). The oxygen would be breathed from a rubber bag, and could be readily and cheaply generated by the use of oxylyth.

TREATMENT OF COMPRESSED AIR ILLNESS.—Recompression.—Recompression, if immediate, is the most effective means at our command for the treatment of decompression symptoms. As Hill put it, "all measures are as nothing, as compared with the efficacy of recompression, by means of which men have truly been raised from the dead."

The first suggestion as to the value of recompression is found in the report made by Pol and Wattelle, on their work at Douchy, in 1854. It will be remembered that they stated among their conclusions: "There is ground for the hope that recompression will relieve symptoms coming on after decompression." Hoppe also suggests recompression as an efficient method for relieving compressed air illness. Workers themselves have found that relief from the often excruciating pains of "bends" was found by reëntering the caisson. It has also been the custom among the Greek sponge divers to descend below the water if they suffered from symptoms after reaching the surface. Smith, in his report on the caisson work on the Brooklyn Bridge, suggested the use of a recompression chamber.

The first medical air-lock was put into operation by E. W. Moir, at the original Hudson River tunnel works, in 1890, and proved its efficacy. Since then a medical air-lock has been part of the essential equipment of caisson works.

F. W. Keays reports that, in the construction of the East River tunnels, recompression relieved 90 per cent. of the 3,067 cases of pain treated, failing to give relief in only 103 of the cases.

Reference has already been made to Hill's experiments, demon-

strating microscopically the presence of bubbles in the capillaries of a frog's web on decompression, and their disappearance when the pressure was raised again. Hill, in his book on "Caisson Sickness," refers to the following among other experiments made by McCloud and himself. A large rabbit was exposed for two hours to an excess pressure of 7 atmospheres, and was then quickly decompressed. In about one minute the rabbit developed severe symptoms (fell on its side with convulsions). The pressure was now quickly raised to 5 atmospheres, by emptying a large compressed air cylinder in the compression chamber. The symptoms, however, continued, and the rabbit soon died. It was evident that there was too much delay in reapplying the pressure, which must be raised as soon as practicable after the onset of symptoms, in order to avoid permanent damage to the nerve-tissues, or a too long stoppage of the circulation by the liberated gas bubbles. The experiment was therefore repeated, using the precaution of reapplying the pressure more rapidly. A cat and a rabbit were saturated to an excess pressure of 7 atmospheres, for four hours. Decompression was made in about five seconds, and, about five seconds later, a large cylinder of compressed air was emptied in the chamber, raising the pressure to about 95 lbs., in two minutes. At the moment of decompression the cat sprang to the window, excited and with widely dilated pupils. It became paralyzed in a few seconds, so that it fell helpless on its side. Its head meanwhile showed a pendulum-like movement from side to side. On recompression, the symptoms gradually disappeared. The pressure was maintained for forty-five minutes and then slowly lowered. Complete recovery set in and on taking the cat from the chamber it appeared to be perfectly normal. The next morning it was normal in every respect. In the case of the rabbit in this experiment, there was no time for any symptoms to develop. It was quite normal on leaving the chamber.

In the diving experiments on the submarine F. 4, a recompression chamber was in readiness on the deck of the diving float. Undoubtedly the use of this chamber saved the life of the diver W. F. L., whose symptoms have previously been described and who remained for three hours and forty-five minutes beneath the surface of the water because his life-line became fouled.

The following is a description of the medical air-lock used in connection with the East River tunnels of the Pennsylvania Railroad. The lock was a cylinder of steel plate, 7 feet in diameter and 21 feet long, with one end dished. The other end was flat, but reinforced by gusset plates, and contained a flanged door, 5 feet 3 inches x 2 feet 4 inches, which served for entrance to the air lock. The cylinder was divided by a bulkhead containing a door, which separated the cylinder into 2 compartments, respectively about 7 feet and 13 feet in length. The first compartment acted as an air-lock by which persons could enter and leave the recompression chamber without disturbing its pressure. The second or larger compartment acted as a recompression

chamber. This, as well as the front compartment, was floored with plank. This compression chamber contained 2 bunks, upon which patients could be placed. Both compartments were furnished with hot water pipes for heating, compressed air pipes and outlet valves, so that the pressure could be raised or lowered from either chamber. The chamber was also furnished with electric lights, thermometer, telephone, clock, pressure-gauge, electric heater. Means for air circulation were also provided, and the pressure could be raised and lowered from the outside as well. Heavy glass windows were placed on a line with both doors so that the patient, pressure-gauge, and thermometers could be watched from the outside.

Keays says: "One who has seen the results of recompression cannot doubt its practical benefit. We can explain the failure of recompression to cure in certain cases by assuming the gas emboli (bubbles) have done permanent injury to the tissues before treatment has been instituted. In general, the sooner recompression is used after the onset of symptoms, the more immediate and permanent the relief will be."

The method of recompression used in the East River tunnel works was to place the patient as soon as practicable in the recompression chamber, and then raise the pressure to the point at which the subject had been working in the tunnel. It was found that while the pains were often relieved by a lower pressure, the results were more likely to be permanent if the full tunnel pressure was employed. As soon as the pressure had reached the full tunnel pressure, decompression was begun, the time of decompression being fully twice as many minutes as there were pounds of pressure.

Keays found that the best results were produced by reducing the pressure rather quickly for the first 10 or 15 lbs., after which point decompression was very slowly effected. If able to do so, the patient was directed to move about during the period of decompression, as it was found that exercise, especially of the affected part, was of assistance in permanent relief.

Occasionally the symptoms returned after the patient had left the lock. In such cases the patient was recompressed a second time. In some instances it took three or four recompressions before permanent relief was secured.

While recompression chambers should always be available in caisson work, they are not always necessary for diving operations. As pointed out in the Report of the Admiralty Committee on Deep Diving, there is always the possibility of sending the diver down again, should he develop symptoms after reaching the surface, or come up from any other cause, or be hauled up more quickly than is safe. As there is usually an interval of some minutes before symptoms due to rapid decompression develop, there would always be time to haul the diver in, ease his valve, and send him down again. The Admiralty Committee states that even if ~~very~~ serious symptoms have already developed, and the diver is helpless, it is far safer to open his valve, give him plenty of air, and

then drop him down slowly and steadily on the life line until he recovers or the bottom is reached. He will probably have recovered by the time he is down a few fathoms. Another diver can then be sent after him shortly. If he has no symptoms as yet, he can go down himself in the ordinary way until a safe depth is reached. In any doubtful case, where it seems possible that symptoms may develop, the diver on coming to the surface might remain in the water or on the diving ladder for ten minutes before coming on board and having his helmet unscrewed. He could thus very easily descend again if he began to feel any symptoms. In coming on board, he should not undress for another twenty minutes.

Ventilation of Caissons.—(1) *Carbon Dioxid.*—As a rule, sufficient air escapes beneath the lower edges of caissons to prevent any excessive accumulation of carbon dioxid from the lungs of the workers. As long as the tension of the carbon dioxid in the air of the caisson does not rise above 1 or 2 per cent. of an atmosphere, no harmful effects can be produced. It should be borne in mind, however, as previously discussed, that as the pressure is increased the carbon dioxid tension must be correspondingly reduced. If, under a pressure of 2 atmospheres in the caisson, the carbon dioxid should accumulate, because of defective ventilation, to the extent of 1 or 2 per cent., such a percentage would have the same effect as 4 or 8 per cent. of carbon dioxid at atmospheric pressure. This would produce severe panting and exertion, hence not only greatly reducing the efficiency of workers, but throwing such additional strain on the circulation as to render the workers liable to symptoms of compressed air illness on decompression. Such accumulations of carbon dioxid are possible during the operation of concreting caissons, after they have been sunk to their bearings, or when the caisson is being driven through water-tight strata, such as clay. Under such circumstances practically no air can escape from the caissons, and the supply of fresh air to the caisson can be very materially reduced.

As Hill points out, there is no need whatever for the excessive air supplies in caissons which are advocated by Snell, who thought that the accumulation of carbon dioxid had a considerable effect in the causation of decompression symptoms. Snell states that an increase in the quantity of carbon dioxid from 0.04 per cent. to .1 per cent. at 30 lbs. pressure is the forerunner of much illness. Snell advocated a ventilation of as much as 12,000 cubic feet per man. As Hill justly observes, the money spent in securing this enormous supply of compressed air could be utilized to far better advantage in cooling and drying the air of caissons and in supplying electric fans to keep the air in circulation. Undoubtedly the decrease in cases of illness which Snell observed consequent to increasing the air supply was due to the fact that the great volumes of air which were forced in produced perceptible drafts in the neighborhood of air supply pipes, great quantities escaping beneath the edges of the caisson. In this way, the circulation of air

was perceptible, resulting in the comfort and diminished exhaustion of the workers. Their better physical conditions at the close of the shift therefore favored prompt desaturation, with a subsequent decrease in the number of men taken ill.

(2) *Deleterious Gases in Caissons.*—Where work is carried on in compressed air, at considerable pressure, the possibility of the formation of carbon monoxid gas in the cylinders of air compressors merits some attention. Owing to the great heat developed during the compression stroke, in air compressors, oil used for lubricating cylinders may flash and produce carbon monoxid gas, due to the fact that it is incompletely consumed. Attention should therefore be given to the quality of oil utilized to lubricate the cylinders of air compressors for the supplying of compressed air for human consumption. Only oils of very high test should be used for this purpose. Castor oil seems to be one of the best lubricants, so far as air-pumps for the use of divers are concerned. French advocates the use of this oil.

Where rocks are encountered in the process of sinking caissons, or in the driving of tunnel-headings through rocky formations, blasting must often be resorted to. The explosion of dynamite liberates gases which under favorable conditions consist of carbon dioxid, nitrogen, and oxygen. Under unfavorable conditions, as, for instance, when the dynamite is damp, or when for any other reason combustion has been incomplete, the gases given off will also contain carbon monoxid, nitrous oxid, methan, hydrogen, and sulphuretted hydrogen. According to Haldane, the amount of carbon monoxid formed may reach 36 per cent. It is well known that carbon monoxid is a colorless, odorless, highly poisonous gas, its poisonous properties being due to its great affinity to the hemoglobin of the blood, which is some 200 times greater than that of oxygen. In this way, an atmosphere containing $1/10$ of 1 per cent. carbon monoxid might be expected to displace 50 per cent. of the oxygen in the blood, thus leading to symptoms of acute oxygen starvation. The presence of the carbon monoxid in the air is imperceptible to the victim, the fact of its presence not being revealed until symptoms of poisoning take place. Loss of consciousness and collapse may follow, after slight feelings of sickness and dizziness. As a rule, the amount of carbon monoxid present after blasting in tunnel-headings constructed by the use of compressed air will not be considerable. As a measure of safety, however, it is well to blow such headings out, after blasting, with air-pipes. The safety of the air may also be tested by exposing small animals, such as mice or canaries, to the air. Because of their high bodily temperature and the great rapidity of their circulation, such small animals are affected by an atmosphere containing carbon monoxid much more rapidly than a man.

DEVICES FOR THE SAFETY AND COMFORT OF WORKERS.—*Gauges.*—Because of the possible onset of symptoms, all air-locks should be provided with gauges, both on the inside and the outside, so that the pressure within the air-lock may be properly controlled. Recording

gauges are also advisable, so that the rate of fall of the pressure and the time spent in decompression may be recorded. All air-locks should be under the supervision of a competent and reliable lock tender, who will carry out to the letter the prescribed methods and times for decompression.

Washrooms and Locker Rooms.—In any considerable compressed air works, suitable washrooms, locker rooms, and barracks should be provided for the use of workers. Compressed air workers should be afforded the fullest opportunity to change their working garments, wet with perspiration, for dry ones, and to enjoy the beneficial stimulus of a bath. Spray shower baths should be provided, furnishing water at a considerable pressure, in the form of a fine spray. Such baths combine the stimulating effects of the cold shower with the agreeable and cleansing properties of hot water. As warm water forcibly thrown in the form of a fine spray possesses the stimulating qualities of water at a lower temperature and at the same time the superior cleansing qualities and comfort of a warm bath, the stimulus to the circulation assists in desaturating the body of the remaining nitrogen in the tissues.

At the close of decompression, wherever the pressures exceed 23 lbs. gauge, barracks should be provided, furnished with suitable cots, in which workers may remain for at least an hour after undergoing decompression, for the purpose of observation. The records of physicians in charge of medical supervision of the personnel in large compressed air works are full of instances in which workers left the caisson apparently in good physical condition only to be picked up later, collapsed, on the street or in some neighboring saloon, suffering from severe decompression symptoms.

CONDITIONS DUE TO DIMINISHED BAROMETRIC PRESSURE

In the preceding section, we have considered the effects of increased barometric pressure upon the organism, the morbid consequences of intensive exposure to such pressure, and means of prevention and treatment.

It now becomes necessary to consider the opposite condition, *viz.*, the effects of exposing man to diminished barometric pressure. In the past, man has been exposed to diminished barometric pressure chiefly in inhabiting and exploring the mountainous regions of the earth, and occasionally in balloon ascensions. The present, and the much greater, impending, future development of aërial navigation will multiply the occasions requiring exposure to diminished barometric pressure and make it even the more important that we should fully understand the effects. Nor is the study of the effects of diminished barometric pressure of importance solely from a practical standpoint, but the study

of these conditions has already thrown much light upon physiological processes, and is placing us in possession of knowledge which has proven of great utility in other fields of medicine.

It has long been a matter of common knowledge that, whenever certain altitudes are exceeded, a train of symptoms ensue which may vary all the way from slight physical discomfort to grave symptoms, perhaps loss of consciousness and even death. Various names have been ascribed to these effects of high altitude, such as "mountain sickness," "Alpine vertigo," and, in South America, "puña" or "soroche" (antimony). The latter term arose from the fanciful belief that the symptoms were caused by poisonous metallic emanations (mountain sickness being common in the lofty mining regions in Peru). We owe, however, to the classic researches of Paul Bert the discovery that the symptoms caused by exposure to diminished atmospheric pressure are in reality due to the lack of the oxygen pressure to which the body is accustomed. In this classic on barometric pressure, Paul Bert reviews the entire literature of the world for data in regard to mountain sickness, and especially the writings of travelers and explorers. He is able to find specific references to the symptoms caused by high altitudes as early as 1596, in Robert Regnault Cauxois's translation of the journeys in South America from 1534 to 1554 of the Jesuit Acosta. It speaks of a sickness "strange and unwonted" which suddenly attacked him in climbing the mountains of Peru.

Until the invention of the balloon we find references to mountain sickness mainly confined to the writings of explorers who, for the most part, contented themselves with referring to the various symptoms which they experienced without going into any scientific discussion of their cause. However, with the enthusiasm, the increased opportunities for scientific observations, and the competition for altitude records which were brought about by the development of the balloon, and subsequently the invention and development of the aeroplane, an increasing volume of scientific observations have been directed to the study of the effects of diminished barometric pressure. At present this is a field of medical research in which our knowledge is both rich and varied.

Symptoms of Mountain Sickness.—There is a wide variation in different individuals in the altitude at which symptoms of the exposure to diminished barometric pressure begin to make their appearance. For most persons the height of 10,000 feet, corresponding to a barometric pressure of 516 millimeters, forms a critical point above which symptoms begin to make their appearance. On the other hand, in susceptible persons, the symptoms may be severe and make their appearance long before the previously mentioned critical altitude of 10,000 feet is reached, and such persons may be so uncomfortable at relatively low levels (say between six and eight thousand feet) that they are forced to return to lower levels.

One of the most graphic accounts of the onset of mountain sickness

by a non-medical writer is that contained in von Tschudi's book,* which is quoted by Paul Bert as follows:

"I was climbing the mountain vigorously, when I felt the formidable influence of the rarefied air; I felt in walking a strange discomfort. I had to halt in order to breathe, even then I could hardly do so; if I tried to walk an indescribable agony seized me. I heard my heart pounding against my ribs: my breathing was short and gasping; I had an enormous weight on my chest. My lips were blue, swollen and fissured; the conjunctival capillaries broke open and from them welled forth a few drops of blood. The sensations were singularly blunted; sight, hearing and touch were affected; before my eyes floated a thick cloud, grayish and often reddish, and I wept blood-stained tears. I felt myself between life and death; my head spun, my senses failed and I stretched myself trembling upon the ground. In truth, had the greatest riches, or immortal glory awaited me a few hundreds of feet farther up, it would have been both physically and morally impossible for me even to have moved my hand in their direction."

The power of adjustment of many individuals is such that they experience no symptoms until an altitude of some 14,000 feet, corresponding to a pressure of 444 millimeters, is reached, while the exceptionally fit and hardy individual may attain an altitude of 18,000 feet, corresponding to a barometric pressure of 382 millimeters, without much discomfort, before symptoms worthy of note are experienced.

The advent of mountain sickness is also notably affected by the manner in which the altitude is reached, *e. g.*, whether the height attained is reached by a slow and arduous climb, or whether the individual is transported thither passively either on horseback or on a train, or in a balloon or aeroplane flight.

Types of Mountain Sickness.—There are two types of mountain sickness, the acute and the chronic.

The *acute* type comes on when the transition from normal to low barometric pressure is abrupt, as when great heights are attained quickly either in a train or in a balloon or aeroplane flight. Generally speaking, the symptoms are characterized by rapid pulse, nausea, vomiting, dimness of vision, dulling of the hearing, buzzing in the ears, bodily weakness, which may reach such a degree as to render the subject incapable of movement, lividity of the skin, loss of consciousness, and death, if the barometric pressure falls too low or the exposure is too prolonged.

The more *chronic* or slow form of mountain sickness is the more usual type, and usually manifests itself when the altitude is reached by the usual process of mountain climbing, and does not greatly exceed the critical level above which symptoms are developed. On reaching such an altitude the individual complains of no symptoms at first, and on being questioned usually states that he feels well. He then occa-

* "Peru, Reiseskizzen aus den Jahren 1838-1842." 2 vol., Saint Gallin, 1846.

sionally experiences dizzy sensations, and spots seem to dance before his eyes, he has momentary dimness of vision, on straightening up quickly after stooping over. Although the subject still feels comparatively comfortable, inspection will usually show more blueness of the lips, gums, the ear-lobes and the finger-nails than is normal. Some hours later feelings of languor and depression begin to make their appearance, and the subject is disinclined to any exertion. The appetite is greatly diminished or is lost. Upon going to bed the subject feels weak and tired and usually has considerable difficulty in going to sleep. On waking up in the morning, after a bad night, there is usually a severe frontal headache which, in some instances, may have developed in the evening of the first day. The disinclination for food is increased to the extent of positive nausea or even vomiting, and on rising from the bed the subject feels distinctly giddy. The face has a dull and heavy expression, and is slightly cyanosed. The eyes are watery. The tongue is coated and the pulse is high, usually over 100. The temperature is normal, or there may be a tendency to a sub-normal temperature, which is manifested by chilly sensations. There are, perhaps, colicky pains in the abdomen; some diarrhea is present; and a tendency to periodic breathing has been noted. The mental efficiency is markedly reduced. The sufferer may show great unreasonableness of temper and may also experience great difficulty in performing mental processes such as multiplication or addition of numbers, which under ordinary circumstances are performed with ease. Barcroft recounts that at the altitude of 11,000 feet he heard two clever and distinguished physiologists pause to discuss whether or not 4×8 equaled 32.

According to the observations of Ravenhill* who was medical officer in the Andes in a mining district over 15,000 feet above sea level, mountain sickness of the normal type may be divided into two types: (1) those in which *cardiac* symptoms predominate; and (2) those in which *nervous* symptoms predominate. As an example of the first type he mentions the case of an Englishman who arrived in the district by train after a forty-two-hour journey from the sea level. This was not his first visit as he had lived there for three months and enjoyed good health all the time. He had also visited other mountainous districts in Peru and had reached an altitude of 17,000 feet without inconvenience. Upon arrival he was apparently in good health and said that he felt quite well, although he remained quiet, did but little and went to bed early. He awoke the next morning with the usual symptoms of mountain sickness. As the day progressed, however, he became very ill; his pulse was very rapid, and respiration reached a rate of 144 and 40 respectively in the afternoon. Later on he was very cyanosed and suffered from acute air-hunger, all the extraordinary muscles of respiration being called into play. The heart sounds were very faint; the pulse was irregular and of small tension. He apparently

* Ravenhill, T. H. "Some Experiences with Mountain Sickness in the Andes," *Jour. Trop. Med.*, London, 1913, xvi, pp. 313-320.

presented a complete clinical picture of a failing heart. This condition persisted through the succeeding night, and was combined with difficulty in coughing up mucus. Inhalations of oxygen, strychnin and digitalis were administered. The patient was somewhat better towards morning and took advantage of an early morning train to return to a lower altitude. He was much better at 12,000 feet and at 7,000 feet was nearly well.

Ravenhill believes that had this patient persisted in remaining at the altitude of 15,000 or 16,000 feet he would have died. Ravenhill also cites the instance of another patient, a young Turk, aged twenty-three, who arrived in that district on July 14th and died on the 19th, after a similar history, the respirations being 60 and the pulse 144, the latter being hardly perceptible when examined by Ravenhill.

In the nervous type described by Ravenhill, the nervous symptoms are most prominent. The simplest form consists in the feeling of exaltation and buoyancy. It has been described as a sense of being lifted in the air as by a balloon. This sensation may precede an attack of mountain sickness of the ordinary type. There may be a tendency to the twitching of the lips and to the trembling of the limbs. While this form generally passes off, the nervous symptoms may be developed to an alarming extent. Ravenhill reports one case of a young Chilean, aged 19, who three days subsequent to his arrival was found to be unable to speak, and to be seized with violent spasmodic movements of the extremities. He resisted examination and was unable to stand or walk. His face was blanched and his lips were almost white, the pupils of his eyes were slightly dilated. Temperature and respiration were normal; the pulse was 140. He had been in this condition practically ever since his arrival, being delirious and talking all kinds of nonsense. He was sent down to a lower altitude the same day and, by the time he had reached the coast, he had completely recovered. So far as the hemorrhages from mucous membranes were said to occur in cases of mountain sickness, Ravenhill states that epistaxis occurred in about 20 per cent. of the cases, but was hardly ever profuse. According to Ravenhill, while this is not very common in those arriving at such high altitudes, it seems to be a common symptom with all those living there when they become ill, especially with any febrile disturbance.

Before passing on to the discussion of the causes of mountain sickness, it is well to point out the dramatic suddenness with which symptoms may make their appearance where the transition to the altitude is continuous and rapid. In the celebrated ascension on September 5, 1862, of Glaisher and Coxwell, the start took place at 1:03; at 1:39 the height of 6,437 meters (21,118.72 feet) was reached; at 1:51, the barometer marked 11.05 inches. Up to this time no difficulty had been experienced by Glaisher in making his observations of the instruments. Glancing at the barometer, he noted that it was but 10 inches, and was descending rapidly. On attempting to use his right arm,

which up to that moment had had all its vigor, he perceived that it had lost all its power and on endeavoring to use his left arm, he found that it likewise was paralyzed. In endeavoring to move his body, he was able to succeed up to a certain point, but it seemed to him that he had no extremities. Trying once more to read the barometer, his head fell upon his left shoulder. Suddenly he felt unable to make any movements whatsoever. He was unable to speak to his companion, Coxwell. First he lost vision, then consciousness. Coxwell, unable to use his arms, pulled the valve cord of the balloon with his teeth and thus brought the aeronauts out of a situation which, if persisted in, would undoubtedly have been fatal to both.

Less fortunate were the results of the ascension of the "Zenith" which took place on April 15, 1875, in which three French aeronauts, Tissandier, Crocé-Spinelli and Sivel, endeavored to break the altitude record, with the result that of the three only Tissandier survived. The following translation from Tissandier's graphic account quoted in Paul Bert's book depicts this voyage in striking fashion and describes the insidious and abrupt onset of the effects of oxygen want at this high altitude.

"I arrive at the fatal hour when we were about to be seized by the terrible influence of low barometric pressure. At 7,000 meters (22,965 feet) we were all standing upright in the balloon basket; Sivel, torpid for a moment, had revived; Crocé-Spinelli is motionless facing me. 'See,' said the latter, 'how beautiful the cirrus clouds are * * * *.' The sky, far from being dark and black, was of a beautiful clear and limpid blue; an ardent sun burned our faces, nevertheless the cold commenced to make its influence felt and we had already before this placed our wraps on our shoulders. Torpidity had seized me, my hands were cold and icy. I wished to put on my fur gloves, but without being aware of it, the effort to take them from my pocket was one which I could not make.

"Nevertheless, at a height of 7,000 meters I write almost mechanically in my note book. I reproduce here the following lines which I wrote without having been actually conscious of writing them. They are written in almost illegible fashion by a hand which the cold must have caused singularly to tremble. 'My hands are frozen. I feel well. We all feel well. There is fog on the horizon with little rounded cirrus clouds. We ascend. Crocé pants. We breathe oxygen. Sivel closes his eyes. I empty the aspirator. The temperature -10° . 1 hr. 20 minutes. $H = 320$. Sivel is dozing. 1 hr. 25 minutes. Temperature -11° . $H = 300$. Sivel throws ballast. Sivel throws ballast.'

"Sivel, indeed, who had remained some instants as though pensive and motionless, closing his eyes sometimes, without doubt having just recalled that he wished to transcend the limits where the 'Zenith' was floating, stood up. His energetic face lit up suddenly with an unaccustomed brightness, and he turned to me and said: 'What is the pres-

sure?' '30 centimeters [7,450 meters (24,442 feet) of altitude].' 'We have much ballast; must we throw it out?' I answered him, 'Do what you wish.' He turns to Crocé with the same question. Crocé nods his head with an energetic sign of affirmation * * * * (Three sacks of ballast were then thrown out).

"But I had always kept my immobility without being aware that I had already lost the power of all movement. At 7,500 meters (24,606 feet) the state of torpidity in which one finds one's self is extraordinary. The body and mind become enfeebled, little by little, gradually, insensibly, without one's being aware of it. There is no suffering; on the contrary one feels an inward joy and, as it were, an effect of the radiation of light in which one is immersed. One becomes indifferent; one thinks no longer either of the perilous situation or of danger. One ascends and is happy in the ascension. The vertigo of the high regions is not an empty word but, in so far as I may judge by my present impressions, this vertigo appears as a last incident. It immediately precedes direct annihilation, sudden, unexpected, irresistible."

When Tissandier recovered consciousness, the balloon was descending with a frightful rapidity and his two companions were in the bottom of the balloon basket. Sivel's face was black, his eyes were glazed and his mouth open and full of blood; Crocé's eyes were half closed and his mouth bleeding. When the balloon finally reached the earth, his two companions were found to be dead.

The Cause of Mountain Sickness.—The cause of mountain sickness is oxygen want. That this condition was the cause of mountain sickness was first suggested by Jourdanet and subsequently demonstrated by Paul Bert. Bert showed that the physiological action of gases on the organism is a function of their partial pressure and not the actual percentage composition of the atmosphere. He found that different animals, such as the cat, when subjected to diminishing barometric pressure succumbed when the partial pressure of the oxygen reached approximately $4\frac{1}{2}$ per cent. of an atmosphere. If in the beginning of the experiment the animal was subjected to only one-half an atmosphere of total pressure, then death came on when the oxygen was reduced to 9 per cent., which again is $4\frac{1}{2}$ per cent. of an atmosphere. We also owe to Paul Bert the first approximately correct estimation of the oxygen dissociation curve for hemoglobin in the blood. As pointed out by Douglas, Haldane, Henderson and Schneider the figures obtained by Bert conform very well with those secured by subsequent observers, and are considerably more accurate than those subsequently obtained by Hüfner. While Bert came to the conclusion that the cause of mountain sickness was entirely due to oxygen want, other observers have endeavored to attribute the symptoms either in whole or in part to causes other than oxygen want. Thus, Mosso believed that the cause of mountain sickness was due to "acapnia," i. e., a diminished carbon dioxide content in the blood; other observers have evolved obviously erroneous

theories which it is unnecessary to discuss here. The symptoms evoked by mountain sickness and other conditions accompanied by oxygen want, such as poisoning by carbon monoxid, are very similar; this is not surprising when we consider that the effect produced on the body cells is the same. In the case of mountain sickness the body cells are not receiving their normal supply of oxygen. Under the prevailing low atmospheric pressure, it is not taken up in adequate amount by the blood, while in carbon-monoxid poisoning the cells are deprived of their oxygen supply because oxyhemoglobin is displaced by carboxy-hemoglobin. The symptoms of mountain sickness, viz., headache, throbbing, nausea, vomiting, fainting, etc., are also experienced in carbon-monoxid poisoning. Douglas, Haldane, Henderson and Schneider point out that if inhalation of carbon monoxid is carried out only to the point of producing slight temporary oxygen want, the headache and nausea often make their appearance after the carbon monoxid has disappeared from the blood and after the oxygen supply to the tissues is practically normal again. In similar fashion, during their observations on Pike's Peak, they found that it was the experience of those visiting the Peak that they often suffered headache on coming down by train after a stay of three or four hours on the summit. Since the symptoms of mountain sickness are produced by oxygen want and by nothing else, some discussion is necessary of the mechanism of the physiological supply of oxygen to the tissues and of the relations of the partial pressure of oxygen in the atmosphere in effecting and maintaining the supply.

MECHANISM OF OXYGEN SUPPLY TO THE TISSUES.—As is well known, the oxygen is carried to the body tissues by the hemoglobin in the red blood-cells. The venous blood as it circulates through the lungs is exposed to the air in the air-cells of the lungs, only a thin membrane intervening. The excess of carbon dioxid with which the venous blood is charged passes out into the alveolar atmosphere and oxygen unites itself to hemoglobin, thus converting the venous into artificial blood. Now the study of the ability of the hemoglobin to take up and to part with oxygen shows that it is one of the most remarkable substances in nature from a physical-chemical standpoint. While it is true that analogies have been attempted between the reactions of hemoglobin with oxygen and certain other chemical reactions, such as, for instance, the union of calcium oxid with carbon dioxid, nevertheless, such reactions are not analogous with the saturation or desaturation of hemoglobin with oxygen according to whether it becomes charged with oxygen in the lungs or gives up this charge to the tissues. Barcroft speculates that were it not for this remarkable quality of hemoglobin "man might never have attained any activity which the lobster does not possess, or, had he done so, it would have been with a body as minute as that of the fly." The properties of hemoglobin in its capacity to unite with oxygen are so remarkable that it is well worth our while to discuss them here briefly. It is well known that hemoglobin is a complex pro-

teid iron-containing substance which has the property when shaken up with oxygen to unite with a definite quantity of the gas, in the proportion of 32 grams (493.82 grains) of oxygen to each 56 grams (864.215 grains) of iron in the hemoglobin when fully saturated. When, however, we examine blood taken from the circulation, we always find it to be combined with a less quantity of oxygen than this. If we take a solution of hemoglobin, remove all the oxygen from it by pumping it out with a vacuum pump and then subsequently shake up a small quantity in closed vessels with oxygen at various pressures,

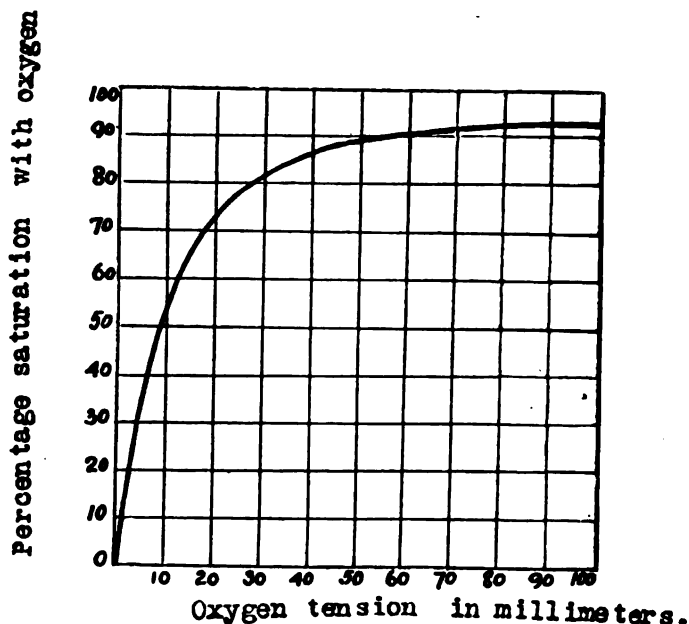


CHART 3.—THE DISSOCIATION CURVE OF PURE HEMOGLOBIN IN THE ABSENCE OF ELECTROLYTES. (After Barcroft.)

for instance from 0 to 100 mm. of oxygen, we will find that as the pressure varies, different quantities of oxygen will be taken up by the hemoglobin solution. If we plot the amounts of oxygen taken up in relation to oxygen pressure, we obtain a curve having the characteristics of a rectangular hyperbola (Chart 3).

This result, however, can be obtained only on condition that the hemoglobin with which we are experimenting is pure hemoglobin and nothing else, all salts of the plasma and all carbon dioxid being absent. An analysis of this curve shows that such a form of curve is unsuited to meet the requirement of the oxygen supply of the body, for while pure hemoglobin takes up oxygen very readily even at low pressures (*i. e.*, at 20 mm. pressure, the hemoglobin would still be approximately 70 per cent. saturated), it holds its oxygen too tenaciously to yield it readily to the tissues. We find, however, that in

the case of the blood itself, the form of this curve which shows the percentage saturation of the pure hemoglobin with oxygen at various oxygen pressures is modified as follows: (a) by the presence of the salts in the blood; (b) by various pressures of carbon dioxid present; and (c) generally speaking, by the hydrogen-ion concentration of the blood. As a result of the numerous investigations which Bohr, Barcroft, Douglas, Haldane and others have carried on, the relation of the degree of saturation of hemoglobin with oxygen in the blood to the oxygen pressure, or as it is termed, the "dissociation curve" of

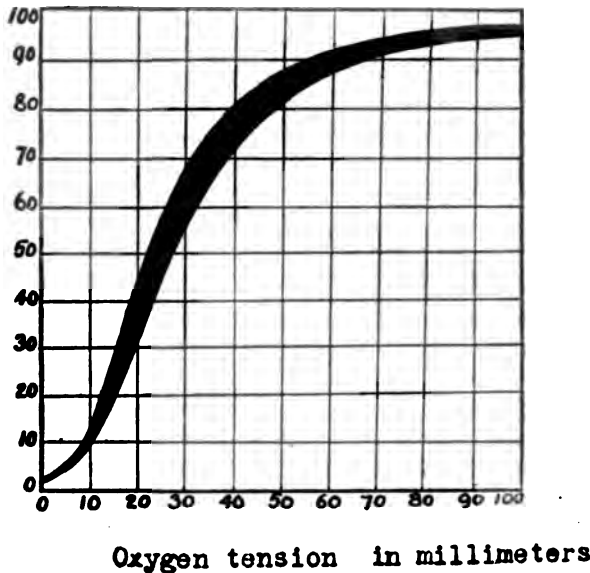


CHART 4.—NORMAL OXYGEN DISSOCIATION CURVE OF HEMOGLOBIN IN BLOOD. The thick line shows the extent of variation of normal curves in individuals. (After Barcroft.)

hemoglobin, is represented by the curve (Chart 4) from Barcroft which shows the limits within which the dissociation curves of normal persons fall.*

It will be seen that this curve is not a hyperbola but an S-shaped curve. It differs from the curve of saturation of pure hemoglobin with oxygen in two main respects: (1) that the percentage saturation is not so great with high oxygen pressures; and (2) oxygen is much more readily given up as the pressure falls. While, therefore, with a given oxygen pressure saturating the blood in the lungs, we do not get such a high percentage of oxygen taken up as in the previous case, on the other hand, the oxygen taken up is very much more readily given up to the tissues where the oxygen pressure is low and in this way the oxygen required for metabolism is more readily made available. It is

* BARCROFT. Respiratory function of the blood. Page 226.

to be observed that this curve which is a composite curve is rather broad and indicates considerable variation in the dissociation curves of normal individuals. The curves of particular individuals may move in either of two directions. Their blood at a given oxygen pressure may take up either more or less oxygen than the normal. Barcroft uses the following nomenclature to express these conditions; when the dissociation curve for a particular individual is above the normal situation, i. e., when at a given oxygen pressure the blood takes up an abnormally great percentage of the total possible load of oxygen, the curve is called "pleonectic"; when it takes up less than the usual percentage of oxygen, it is "mionectic"; and when it becomes saturated to the normal extent, it is "mesectic." * The presence of both salts and acids has a similar effect on the oxygen dissociation curve of hemoglobin, but the effect of acids is more marked than that of salts. Investigation has shown that this effect is due to the hydrogen ions present. The physiological importance of this modification is obvious. All cells produce carbon dioxid in activity, and as a result of muscular exertion lactic acid is formed. The presence of both of these facilitates the transfer of oxygen to active body cells.

Christianson, Douglas and Haldane have shown that reduced hemoglobin can take up one-tenth more carbon dioxid than hemoglobin fully saturated with oxygen. For this reason venous blood can take up more carbon dioxid at the same tension than can arterial blood. Since the affinity of hemoglobin for carbon dioxid diminishes as it absorbs oxygen, the carbon dioxid present in the venous blood is more readily given up in the lungs. Therefore, each gas assists in driving off the other. The form of this dissociation curve has been found to be related to the concentration of hydrogen ions in the blood, so that it may be used as an indicator for changes occurring in the hydrogen concentration in the blood, either as the result of exercise, of oxygen want, or of pathological states of so-called "acidosis."

Can this curve be expressed by any mathematical formula? The rectangular hyperbolic form of the dissociation curve of pure hemoglobin free from salts or acids would indicate that there is no clumping or aggregation of the separate molecules of hemoglobin with separate molecules of oxygen. Since, however, the hemoglobin is in colloidal solution, and we know that in such solutions the presence of electrolytes has a powerful effect in causing aggregation or clumping of individual molecules, we may readily suppose that in hemoglobin, as present in the blood, this aggregation or clumping of molecules would account for the difference between the dissociation curve of normal blood and that of hemoglobin. On the supposition that the aggregation or clumping of molecules in hemoglobin causes the reaction to become of a higher

* Barcroft gives as a derivation of these adjectives the Greek word "Pleonektikos," disposed to take more than one's share, from "Pleonexia," a disposition to take more than one's share.

order than unimolecular, A. V. Hill has arrived at an expression for this curve in the following formula:

$$\frac{y}{100} = \frac{kx^n}{1 + kx^n}$$

where y is percentage of saturation of hemoglobin with oxygen and x is the oxygen pressure. This formula has been found to apply in practice if proper choice is made of values for the constants k and n . While Hill did not attach any direct physical meaning to these constants, Barcroft regards k as the equilibrium constant, and n as the average number of molecules of hemoglobin aggregated together. By experimental observations it seems probable that the value of n is approximately 2.5. This value of n has been found to be remarkably constant in the presence of different concentrations of carbon dioxid. In this connection Barcroft remarks that "since n remains so constant it is probably the expression of some definite physical fact."

According to Bayliss this seems to be about as far as we can go at present. The apparent constancy of the value for n leads Barcroft to believe that changes in the amount of acid present do not change the number of molecules in the hemoglobin aggregates, but produce changes in k , the equilibrium constant. While, therefore, this gives us a useful working formula, expressive of the dissociation curve of hemoglobin, according to Bayliss, more work is necessary before we can regard the nature of the dissociation between oxygen and hemoglobin as settled. Bayliss suggests that further investigations are well worth while as to whether oxygen is absorbed instead of being chemically combined with hemoglobin.

The Lungs.—We have just seen how, through the unique property of hemoglobin, oxygen is conveyed to the tissues in far greater quantity than if it were merely dissolved in the blood-plasma, and how oxy-hemoglobin parts with its oxygen at places in the body where the existing tension of oxygen gas is lower than at the point at which the hemoglobin took up its oxygen in the first place. In order to understand better the conditions of oxygen supply to the body which must be met under conditions of lowered atmospheric pressure, we must discuss the mechanism by which hemoglobin, after having given up the major part of its oxygen to the tissues, renews its supply from the external air, and at the same time gets rid of the carbon dioxid which has been given off to the hemoglobin by the cells. It is well known that carbon dioxid is transported from the tissues almost entirely by hemoglobin, the same substance which supplies the tissues with oxygen. Man, in common with other air-breathing animals, has an arrangement, the lungs, by which a large surface of blood is brought into contact with air, a thin membrane intervening between the blood and the air. This air is repeatedly changed by the process of breathing. The distance, there-

fore, through which the gases have to diffuse is extremely small. The air with which the blood is brought in contact is that contained in the sac-like terminations of the branching air tubes of the lungs, the pulmonary alveoli. Since it is mechanically impossible to empty all the air from the lungs, the air in these sacs is renewed by process of diffusion with the inspired air. Since oxygen is constantly being absorbed from it by the blood and carbon dioxid given out, this air contains oxygen at a lower pressure than the external air and carbon dioxid at a much higher tension than the external atmosphere. It is the alveolar air which actually takes part in the exchange of gases from the blood. Under ordinary conditions, at sea level, the composition of alveolar air is approximately from 13 to 14 per cent. of oxygen and from 5.5 to 6 per cent. of carbon dioxid. The approximate tension of the oxygen (allowing for the tension of water-vapor with which alveolar air is saturated) is 100 mm., while part of the carbon dioxid is 40 mm. This 100 mm. represents the pressure head under which oxygen enters the blood under ordinary conditions.

We may now discuss the physiological adaptations wrought in the body by exposure to diminished oxygen tension. These are:

- (a) Changes in the respiration.
- (b) Changes in the circulation.
- (c) Changes in blood concentration.
- (d) Possible changes in the oxygen tension of arterial blood.
- (e) Changes in the acid-alkali balance of the blood.

CHANGES IN THE RESPIRATION BROUGHT ABOUT BY EXPOSURE TO DIMINISHED ATMOSPHERIC PRESSURE.—One of the most striking experiences of those obtaining high altitudes is the excessive panting which accompanies physical exertion. This panting is undoubtedly caused by a demand for oxygen in the body, and is a compensatory phenomenon. As is well known, under ordinary conditions the breathing is so regulated as to maintain the tension of the carbon dioxid in the alveolar air at a constant level (about 40 mm. for adults). Under ordinary conditions upon muscular exertion the amount of carbon dioxid carried to the lungs by the blood is very greatly increased, and therefore there is an increase both in the number and in the volume of respiration in order that the excess of carbon dioxid brought by the blood may be carried away.

We have seen that under ordinary conditions with a tension of about 40 mm. of carbon dioxid in the alveolar air, the corresponding oxygen tension of the air is about 100 mm. or approximately 13 per cent. of an atmosphere. While the changes in the hydrogen-ion concentration of the blood is the fundamental factor in exciting the respiratory center, under ordinary conditions respiration is regulated by the tension of carbon dioxid in the blood, changes of which produce variations in the hydrogen-ion concentration. There is such relation between the ventilation of the lungs, the excretion of carbon dioxid and the oxygen needs of the

body as to maintain the tension of the carbon dioxide in the alveolar air at approximately the level noted above (40 mm.). When, however, there is increased demand for oxygen by increasing the ventilation of the lungs, we may not only wash out more rapidly the excess of carbon dioxide, as in the case of muscular exertion, but the increased ventilation will raise the tension of the oxygen in the alveolar air. Since the atmospheric air contains only 21 per cent. oxygen, it is possible by any rate of pulmonary ventilation to raise the percentage of oxygen in the alveolar air up to more than approximately 19 per cent. Since this is the case, it is evident that there is a limit to the extent to which increase in pulmonary ventilation may be counted on to raise the tension of the oxygen in the alveolar air of the lungs. Thus at an altitude of 14,000 feet (a barometric pressure of 460 mm.), the oxygen tension in the external air would be one-fifth of the barometric pressure, or 92 mm., and the utmost obtainable oxygen pressure in the lungs by the process of pulmonary ventilation could not exceed about 75 mm. (allowing for the pressure of water vapor in fully saturated air), and this pressure could be obtained only as a result of extraordinary panting which could not be maintained for any length of time. Observations show that at this elevation, the oxygen tension in the alveolar air is very far short of this level. Thus, Douglas, Haldane, Henderson and Schneider found that the tension of oxygen in the alveolar air at the summit of Pike's Peak averaged from about 53 to 56 mm. It is known that at sea level the percentage of carbon dioxide in the alveolar air remains approximately constant under all conditions. If, on increasing our altitude, the tension of carbon dioxide in the alveolar air were to remain constant at 40 mm., the percentage of carbon dioxide in the alveolar air would increase as the barometric pressure decreased. With increases in altitude this percentage of carbon dioxide would be so great as to lower the tension of oxygen to a point where the blood would be prevented from obtaining an adequate load of oxygen. We therefore find a fall in the tension of the carbon dioxide in the alveolar air as the altitude increases. Thus, in the experiments in re-breathing in the low pressure chamber conducted by the Medical Air Service in the U.S.A., it was found that in passing from normal atmospheric pressure of 760 mm. to that of 350 mm., corresponding to an altitude of 20,000 feet, the oxygen tension of the alveolar air of eight subjects fell from 102 mm. Hg to 35.8 mm., an average fall of 68.8 mm., while the tension of the carbon dioxide decreased from 42.6 mm. to 34.1 mm., an average fall of 8.5 mm.

In the case of the observations on Pike's Peak, the oxygen tension of Haldane's alveolar air fell from 100.4 mm. at sea level to 48.6 mm. (4 hours after arrival), and subsequently arose to a maximum of 55.5 after a sojourn of fifteen days. The tension of his alveolar carbon dioxide fell from an average of 39.6 mm. at sea level to 32.2 mm. immediately upon arrival, and to 25.6 mm. after a similar sojourn. This progressive fall in the alveolar carbon dioxide tension of course corresponds to a corresponding increase in the ventilation of the lungs. The

normal resting adult breathes an average of $7\frac{1}{2}$ liters (7.92 quarts) a minute, and the volume of each respiration is from 350 to 600 c.c. Thus Haldane obtained as the average ventilation of his lungs the following: while resting in bed at sea level, 7.67 liters per minute; on Pike's Peak, under the same conditions, 10.21 liters per minute; at sea level, while standing, 10.40 liters per minute; on Pike's Peak, while standing, 14.89 liters per minute; at sea level, walking two miles per hour on grass, 18.6 liters per minute; on Pike's Peak, walking two miles per hour, 27.9 liters per minute; at sea level, walking four miles per hour on grass, 37.3 liters per minute; on Pike's Peak, walking four miles per hour, 57 liters per minute; at sea level, walking five miles per hour on grass, 60.0 liters per minute; and on Pike's Peak, walking five miles per hour on grass, 110.2 liters per minute.

If these values are related to the amount of carbon dioxid given off, it is found that on Pike's Peak the volume breathed per cubic centimeter of carbon dioxid given off was about 27 per cent. greater during rest in bed, 31 per cent. greater during rest standing, 50 per cent. greater during a walk up the level at rates up to about four and one-half miles per hour, and nearly 100 per cent. greater on more severe exertion. In the resting subject this increase of from 30 to 50 per cent. in the air breathed does not attract the attention of the individual. It becomes very evident, however, that on physical exertion in high altitudes the amounts of air taken in at each breath are about a maximum irrespective of altitude, so that the great increase in the ventilation of the lungs is brought about, not by increase in the amount of air taken in at each breath, but by the rate of breathing. The severe panting experienced by all on physical exertion at high altitudes, therefore, becomes inevitable.

While undoubtedly the phenomenon of increased ventilation of the lungs as barometric pressure diminishes serves as a part of the compensatory mechanism to enable the body to obtain oxygen under conditions of increasing difficulty, simple increase in the rate of breathing is by no means sufficient to enable the fullest possible degrees of adaptation to be obtained. Mosso laid great stress upon the fall of the carbon dioxid pressure in the alveolar air because this would be an index of lowered carbon dioxid tension throughout the body generally. Since the reduction of carbon dioxid tension in the blood, all other things being equal, increases its affinity for oxygen, this by itself would be of material advantage in meeting conditions imposed by diminished barometric pressure. The diminution of the carbon dioxid tension would have the effect of increasing the alkalinity of the blood; this explains its greater affinity for oxygen. We are met here, however, with the difficulty that the greater oxygen affinity caused by the alkalins would be more than offset by the reluctance with which hemoglobin parts with oxygen under conditions of diminished acidity. However, careful studies of the dissociation curve of the blood for oxygen by Barcroft and others show that this greater affinity of the blood for oxygen in the

presence of lowered carbon dioxid tension incident to sojourn at high altitudes does not take place, and suggest that the missing carbon dioxid has been replaced by other substances, so that the acid-alkali balance of the blood is maintained at a constant level. Indeed, careful measurements have shown that under conditions of low barometric pressure, the increase in acid is slightly in excess of the loss of carbon dioxid. This increase in acid, while it would lower the affinity of the blood for oxygen, on the other hand would enable it to give up oxygen with greater readiness to the tissues, and this is, after all, the change which we desire to effect, as any slight loss in the affinity of the blood for oxygen can readily be compensated for by the great variations which can be had in the rate of circulation.

Periodic Breathing at High Altitudes.—Besides the increase in the rate of breathing in the lungs, there is one other tendency which we must mention and that is the tendency to periodic breathing at high altitudes. This type of breathing is frequently observed and is more marked in certain individuals than in others. In this type of breathing, the respirations occur in groups of three or four breaths, each succeeding breath being deeper than the preceding one, the interval between each group being marked by a pause. Again, the periodic breathing may occur in cycles of from six to ten breaths, each increasing in depth up to a certain point, after which the breathing again progressively diminishes, no pause, however, occurring. This type of breathing is especially marked on arriving at a high altitude, and tends to disappear as the process of acclimatization is effected. The respiration of oxygen will also abolish the periodic breathing. In those who have become more or less acclimated, this type of breathing disappears, but will often make its reappearance upon any exertion or upon holding the breath.

In this connection, it should be remarked that the ability to hold one's breath is markedly diminished at high altitudes, especially as the process of acclimatization becomes advanced. It has been suggested that the ability to hold the breath decreases as the acidity of the blood increases.

CHANGES IN THE BLOOD.—The blood reacts to diminished barometric pressure by an increase in the amount of hemoglobin present. It was first predicted and subsequently found by Paul Bert that one of the effects of continued exposure to diminished barometric pressure would be an increase in the hemoglobin of the blood. Subsequent observations have shown that this is true. More remarkable is the fact that these changes in the hemoglobin content of the blood are very rapidly produced. Thus in the low pressure chamber experiments made by the Medical Service of the Division of Military Aeronautics of the U. S. Army, it was found that an exposure of only two or two and one-half hours in the low pressure chamber produces changes in the concentration of hemoglobin of as much as 9½ per cent. As a result of these experiments, it was found that at least 25 per cent. of all men showed a well-defined increase in the percentage of hemoglobin, and the majority

showed some evidence of concentration. In those residing continuously at a high altitude, these changes in concentration of the hemoglobin become very marked. Thus, H. H. R., who resided on Pike's Peak (14,000 feet) for a period of several months, showed a hemoglobin percentage of from 144 to 146 with 7,700,000 to 7,500,000 red blood-cells per cubic centimeter. Douglas, Haldane, Henderson and Schneider showed increase in their own hemoglobin in the neighborhood of from 18 to 19 per cent. after a month's residence on Pike's Peak. The following chart from Douglas, Haldane, Henderson and Schneider shows the march in the increase in the hemoglobin of Mr. J. Richards, mining engineer, in passing from sea level to the management of a mine at Paraña, Bolivia, at an altitude of 15,000 feet above the sea, where after a residence of three months the hemoglobin reached a level of 146.

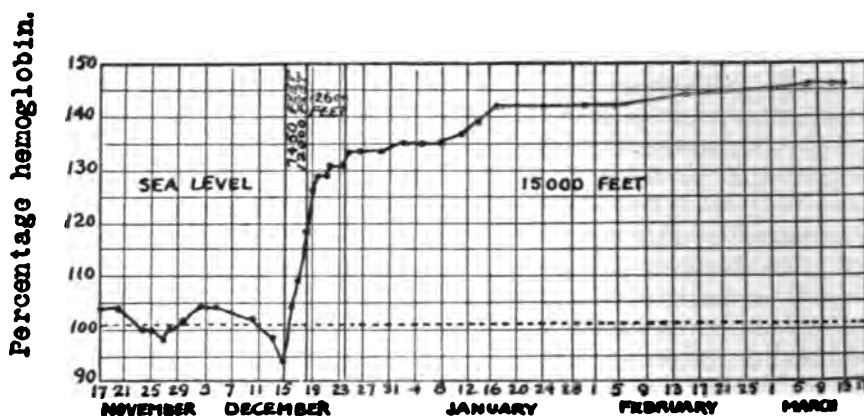


CHART 5.—PROGRESS IN THE INCREASE OF PERCENTAGE OF HEMOGLOBIN BROUGHT ABOUT BY SOJOURN IN HIGH ALTITUDES. (After Douglas, Haldane, Henderson and Schneider.)

Since these changes in the concentration of hemoglobin make their appearance very rapidly, one cannot suppose that they are produced by any immediate increase in the actual number of red blood-cells. The early evidence of hemoglobin percentage, therefore, can be produced only in two ways: (1) by an increase in the concentration of the blood, owing to a diminution of its volume; and (2) by the mobilization in the general circulation of red blood-cells which, under ordinary circumstances, are retained in the byways of the body. Thus, Schneider and Hagans state that abdominal massage and physical exertion often at low altitudes will cause an increase in the number of red cells in the hemoglobin in the peripheral capillaries, whereas in persons acclimatized to high altitudes abdominal massage produces no change (except a frequent lowering) in the contents of hemoglobin and red blood corpuscles; physical exertion fails to increase it. It would appear that the initial increase in hemoglobin observed at high altitudes at first is due in part

to concentration of the blood, and in part to mobilization of dormant red blood-cells. The later changes are due to active formation of new blood elements. Thus Lequer found that dogs, bled to the extent of half their hemoglobin, regenerated fully in about 16 days on Monte Rosa, whereas at a lower altitude about 27 days were required before restoration after a similar hemorrhage.

The natural effect of this increase in hemoglobin is to increase considerably the oxygen capacity of the blood, thus we note that in the Pike's Peak experiments the increase in the total oxygen capacity of the blood in the case of Haldane was 21 per cent.; in the case of Henderson from 35 to 40 per cent.; and in the case of Schneider about 27 per cent. It can readily be seen that these changes in the hemoglobin of the blood must be an important factor in the process of adaptation to life at low barometric pressures.

CHANGES IN THE CIRCULATION.—As is well known, the rate of circulation in the human body may be subjected to great changes. Thus while a round of circulation takes place in about one minute in the resting individual, under severe muscular exertion the time of a round may be reduced to ten seconds. Moreover, the dilatation of the blood-vessels and capillaries may enormously increase the amount of blood-flow through a part. The circulatory mechanism of the body is very sensitive to oxygen demand, the call for oxygen by the various cells of the body being responded to rapidly, and the flow through the tissues requiring an increased supply is itself greatly increased. We thus find the circulation playing a very important part in meeting the difficulties of supplying oxygen in the face of diminishing barometric pressure. The strain thrown upon the circulation in meeting these demands when they are severe also points to the explanation why it is that persons with cardiac defects are unable to adapt themselves satisfactorily to the conditions of life at diminished barometric pressure.

The changes in the circulation due to diminished barometric pressure are reflected in the pulse-rate, the arterial pressures, the capillary pressure, and the venous blood-pressure. Some work has also been done in the way of determining, indirectly, the output of the heart for each beat, and the rate of blood-flow through the lungs and other tissues.

The Pulse-rate.—The acceleration of the pulse due to exposure to low barometric pressures is one of the most conspicuous of the responses to diminished barometric pressure. In the studies made by the Medical Service of the Division of Aeronautics, U. S. Army, during the war, it was found that a study of the pulse-rate during exposure to low oxygen pressures gave a definite indication of the sensitiveness of the organism to low oxygen tension, provided care was taken at the beginning of the experiment to have the subject quiet and calm. The response of the circulation to diminishing barometric pressure is especially important in the case of aviators, as in flying they are transported rapidly to high elevations and the adaptation made to the existing low barometric pressure must therefore be brought about by the emergency adaptive

mechanism of the body without a process of acclimatization being called into play. As a result of a careful study by the Service of the reaction of the pulse to barometric pressure, it was found that in a very few individuals the rate of heart beat began to accelerate when the oxygen was reduced only to 17.5 per cent. (5,000 feet altitude).

In a group of 70 individuals the following reactions were observed:

- 1 per cent. began to react between 7,000 and 8,000 feet (15½ per cent. oxygen).
- 12 per cent. began to react between 8,000 and 9,000 feet (from 15.5 to 14.9 per cent. oxygen).
- 20 per cent. began to react between 9,000 and 10,000 feet (from 14.9 to 14.2 per cent. oxygen).
- 14 per cent. began to react between 10,000 and 11,000 feet (from 14 to 13.7 per cent. oxygen).
- 23 per cent. began to react between 11,000 and 12,000 feet (from 13.7 to 13.2 per cent. oxygen).
- 20 per cent. began to react between 12,000 and 13,000 feet (from 13.2 to 12.7 per cent. oxygen).
- 6 per cent. began to react between 13,000 and 14,000 feet (from 12.7 to 12.2 per cent. oxygen).

The increase noted in the heart beat is at first only from one to three beats per minute, but as the oxygen tension progressively decreases, a greater increase in the rate is likely to occur for each successive diminution in the oxygen. A very marked increase in the acceleration in the pulse takes place as the oxygen tension falls from 13 to 9 per cent. of an atmosphere. In certain individuals, after the more rapid acceleration of the pulse sets in, a satisfactory increase in the rate takes place down even to 6½ or 6 per cent. of oxygen, while in others after a period of rapid acceleration, the rate of the acceleration becomes less for each decrement of oxygen. This decrease in the rate of acceleration suggests that for such individuals the maximum of adaptation has been reached. Some individuals after reacting with good acceleration soon reach a rate beyond which decrease in the oxygen tension will produce no further acceleration. In such cases the heart, after beating at a fixed rate, begins to slow, a sure indication that the limit of adaptation has been reached.

In these experiments it was found that a total increase of from fifteen to forty beats in the heart rate during a test in which the oxygen was lowered to between 7½ and 6½ per cent. of an atmosphere, constituted a good reaction to oxygen want. A failure to react in the pulse-beat may mean either inability to compensate for low oxygen pressure, or it may indicate that the situation has been met in other ways, either through increased ventilation or concentration of the blood. The general experience was, however, that the failure of the pulse-rate to react was an indication of poor toleration of low oxygen tension.

An acceleration of more than forty beats in the heart rate was indicative of too great a strain on the circulation and was met with only in men who did not tolerate well low percentages of oxygen.

Blood-pressure.—The changes produced in the blood-pressure by exposure to diminished barometric pressure are by no means striking. A little reflection shows clearly why this is so.

We have seen that the pulse-rate is a rather sensitive indicator of the response of the body to oxygen want. We must consider the fact, too, that when there is a call for oxygen in the tissues there is a dilatation of the arterioles and thus an increase in the amount of blood brought to the tissues. We would expect that the blood-pressure at the level characteristic of the individual would be maintained at more or less its normal level so long as the circulatory system was adequately meeting the demands upon it in maintaining circulation. So long as good compensation is maintained, there should be no striking changes in either the systolic or the diastolic blood-pressures. The Army studies previously referred to showed certain definite trends of the effect of low oxygen tensions on the circulation with regard to the systolic or diastolic blood-pressures. The systolic pressure maintained its normal level in the majority of cases; in 25 per cent. of the cases a rise occurred during the first part of the experiment, and a gradual fall was noted as the experiment proceeded. In others a gradual fall began soon after the desired altitude was attained. So far as the diastolic pressure is concerned, this usually fell gradually from 4 to 28 mm. while the subject was being held at a given low oxygen tension. In many experiments, as time went by, the diastolic pressure tended to return to the normal. In other cases the diastolic pressure continued to fall gradually throughout the entire experiment. In a few men the pressure was unaltered by the low oxygen tension. It follows that the pulse pressure usually increased during the time of holding at low oxygen tension as the changes in the pulse pressure are inverse to the diastolic pressure. In subjects who reacted poorly, both the systolic and the diastolic pressures fell, the diastolic pressure falling greatly immediately before the subject became entirely inefficient. Since on the one hand, therefore, we have (1) rather satisfactory maintenance of the systolic and diastolic blood-pressures, (2) a very definite acceleration of the pulse-rate, (3) a very pronounced diminution of peripheral resistance because of dilatation of the arterioles and capillaries in order to supply the tissues with more oxygen through an increased blood supply, it is justifiable to assume that the output of the heart per minute is very definitely increased during exposure to diminished barometric pressure. Confirmatory evidence of this is shown by the observations of Schneider and Cisco on Pike's Peak where by the use of Stuart's hand colorimeter they determined that the circulation in the hands of subjects which they observed was increased from 50 to 70 per cent.

CORRELATION OF THE COMPENSATORY FACTORS.—We have seen from the foregoing that three of the main responses to diminished barometric pressure are:

- (1.) Increase in the ventilation of the lungs.
- (2.) Increase in the pulse-rate.
- (3.) Increase in the hemoglobin content of the blood: through (a) concentration at first, and (b) through formation of new blood elements.

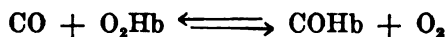
Studies made by Gregg, Lutz and Schneider at the Medical Research Laboratory of the Army Air Service at Mineola, New York, show that the variations that are produced in the reactions to low barometric pressure in different individuals are related to the relative prominence of each of these responses. Thus, with rapid concentration of the blood and the rise in its hemoglobin content, we may get a less decided response to diminished oxygen tension in the way of increased pulse-rate and increased ventilation of the lungs. Again, in cases where the response was characterized by an abnormal increase in the pulse-rate, the evidence of concentration of the hemoglobin did not take place. Other subjects produced an unusual amount of compensation by raising the tension of the oxygen in the alveoli of the lungs by excessive pulmonary ventilation, nor was the response constant on all occasions for the same individuals, as the records of the experiment show that one individual at least reacted in a different way on each of four separate occasions.

Gregg, Lutz and Schneider classify the compensation during exposure to low oxygen tension as follows: (a) Those in which the pulse, after maintaining a high rate for a while, retards slowly and the percentage of hemoglobin increases; (b) those in which the pulse, after a preliminary rise, maintained a constant rate while the hemoglobin increased; (c) those in which the pulse-rate, after the preliminary rise, remained constant and in which the hemoglobin did not increase; (d) those in which the pulse-rate, after a preliminary rise, retarded and the hemoglobin did not increase. They give the following percentage of these various classes of reactors: (a) 55 per cent.; (b) 19 per cent.; (c) 17 per cent.; and (d) 9 per cent. They point out that the interdependence of the three compensatory reactions was shown also in a few cases in which the increase in the pulmonary ventilation, following a period of equilibrium in circulation and respiration, resulted in a retardation in pulse-rate and blood-flow.

THE ARTERIAL OXYGEN TENSION IN EXPOSURE TO THE DIMINISHED BAROMETRIC PRESSURE.—Up to the present time we have considered the respiratory and circulatory response to diminution in the barometric pressure and have considered that whatever the call for oxygen by the body cells, the blood took up in the lungs all the oxygen it could obtain by a process of simple diffusion through the epithelium lining the alveoli of the lungs, increased pulmonary ventilation bringing about a reduction in the tension of the carbon dioxid present in the alveolar air and making available for the process of diffusion a larger proportion of existing oxygen tension.

When the tension of the blood gases was investigated by aëroto-

nometric methods by the physiologists of the Bonn School, no other view was held than that the blood obtained its load of oxygen by a process of simple diffusion through the pulmonary epithelium. Bohr, as the result of some experiments in which he apparently found that there was a greater pressure of oxygen in the arterial blood than in the alveolar air and conversely a greater pressure of carbonic acid in the alveolar air than in the arterial blood, put forth the theory that instead of a simple process of diffusion being called into play, the pulmonary epithelium had the ability to actively secrete oxygen inwards into the blood, and to excrete carbon dioxid into the alveolar air of the lungs. Further, by a mathematical analysis of the process of diffusion through a moist membrane, Bohr arrived at the conclusion that with diffusion alone a difference of pressure of at least 25 mm. on opposite sides of the membrane would be required. Under these circumstances, the diffusion theory would be inadequate to account for the oxygen consumption of the body under all conditions. Now there is nothing inherently improbable in this theory of Bohr's, as physiologists are well acquainted with other analogous processes, as for instance the secretion of oxygen by the epithelium of the swim bladder of fishes, *e. g.*, the swim bladder of the cod fish, if emptied, gradually refills and the gas on analysis contains some 80 per cent. of oxygen. If, as Barcroft remarks, the swim bladder of the cod fish has this power, if the cells of the stomach can secrete hydrochloric acid, there is no reason why the epithelium of the lungs should not secrete oxygen. Of course, those who are in favor of the diffusion theory proclaim that simple diffusion is inherently the more probable because to their minds it is the simpler process, yet to the biologist it would seem just as probable that certain cells of the body should take on specialized functions as that they should act as pieces of inert animal membrane. The oxygen secretion theory has received further impetus by the work of Haldane and Lorraine Smith, and subsequently by Haldane and Douglas. This work has had great influence on physiological thought in the past decade. In their method of investigating the oxygen arterial tension, Haldane and Lorraine Smith made use of the following facts. If hemoglobin is exposed to a mixture of carbon monoxid and oxygen, oxy- and carbo-oxyhemoglobin will be formed in proportion to the relative tensions of oxygen and carbon monoxid. In other words, there is a balanced reaction, thus:



If any three of these quantities can be determined, the fourth can be calculated. In the method developed by Haldane and Douglas a known amount of carbon monoxid is administered by a special apparatus, enough to saturate the blood of the subject to approximately 20 or 21 per cent. The subject then breathes into a closed space, arranged on the Regnault-Reiset principle, by which the carbon dioxid is absorbed as it is exhaled, and oxygen is automatically added to make up for that used by the subject. As carbon monoxid, except for its

affinity for hemoglobin, is physiologically inert, and therefore diffuses indifferently backwards and forwards through the pulmonary epithelium, in a short while the tension of the carbon monoxid in the blood and that in the air in the closed space which is being breathed into by the subject will come to an equilibrium. A sample of blood is then taken from the subject, defibrinated, and a small portion of it exposed to the air of a saturating chamber which is filled with the air that the subject has been breathing plus an amount of carbon dioxid to make the tension of carbon dioxid in the air of the saturating chamber equal to that in the subject's alveolar air, as determined by examining a sample of the alveolar air. Since the percentage of carboxyhemoglobin present in the blood at a given tension of that gas is dependent upon the tension of oxygen in the blood, a little reflection will show us that if the blood exposed in the saturator takes up a greater percentage of carbon monoxid than is present in the blood examined immediately upon withdrawal from the individual, then the oxygen tension of the arterial blood must be higher than that in the alveolar air, and conversely if the percentage of carboxyhemoglobin is greater in the sample from a subject than in the blood exposed in the saturator, then the oxygen tension of the arterial blood is lower than that of the inspired air. Using this method, Haldane and Douglas obtained evidence that under conditions of oxygen demand such as those produced by prolonged muscular work, inhalation of carbon monoxid or exposure to low oxygen pressure, secretory action of the pulmonary epithelium took place.

In the meantime, Krogh by his beautifully devised micro-aërotonometric methods, had shown that Bohr had been in error in his analysis of the physical laws governing diffusion through the pulmonary epithelium and instead of 25 mm. of available oxygen tension being absorbed in the process of diffusion, that this number was relatively small, somewhere in the neighborhood of 2 or 3 mm. In the meantime, Haldane and his co-workers had revised their view to the extent that they did not believe any active secretion of oxygen by the pulmonary epithelium took place under ordinary circumstances, but that this secretory activity was called into play (*a*) either when unusual demands were made for oxygen by the body, or (*b*) when difficulties existed in furnishing an adequate supply. Thus by the carbon monoxid method they obtained no evidence of oxygen secretion by the pulmonary epithelium when the body was at rest or when the air breathed contained a high percentage of oxygen. On the other hand oxygen secretion is evidenced by increase in tension of the oxygen in the arterial blood either when low percentages of oxygen were breathed or when severe muscular work was being performed. Further evidence of oxygen secretion under conditions of oxygen want was obtained by the result of Douglas, Haldane, Henderson and Schneider on Pike's Peak where, using this method, they found consistent evidence of oxygen secretion as shown by the following figures which are culled from their tables:

TABLE III. EXPERIMENTS ON ARTERIAL OXYGEN PUMPING OF MEN

[illegible]

¹ = CO₂ added to saturator to 7.02%.
² = CO₂ added to saturator to 4.70%.
³ = CO₂ added to saturator to 4.64%.
 The figures in brackets are calculated values.

On the other hand, recent evidence would tend to show that the question of active oxygen secretion by the pulmonary epithelium must still be regarded as *sub judice*. In the experiments referred to of Haldane and Douglas, and of Douglas, Haldane, Henderson and Schneider, the degree of saturation of carbon monoxid in the blood was determined by Haldane's method of carmine titration. There are those who speak lightly of colorimetric methods and many scientific workers are disposed to look askance at the result of colorimetric determinations because of the large personal equation involved. Yet the results obtained by Haldane and his co-workers with his carmine titration method have been uniformly consistent, readily reproducible and the values obtained all lie on curves with definite mathematical formulæ, so that the method in their hands must be regarded with great respect. Hartridge has developed a method for determining the percentage saturation of blood with carbon monoxid by the use of a spectroscopic device. In this method the percentage of carbon monoxid present in the blood is determined by the amount of displacement of the α band in the absorption spectrum of hemoglobin, as carbon monoxid is taken up by the blood. In Hartridge's spectroscopic device, the light after passing through the sample of blood to be examined, is so treated as to produce two spectra in reverse direction, one immediately below the other, so that in the case of oxyhemoglobin the α bands of absorption in the two spectra may be set in exact registry with each other. In proportion to the carbon monoxid present these bands become displaced, one to the right and the other to the left. On causing them to coincide again by appropriate adjustment, the amount of travel required can be read off on a micrometer; the excursion registered is a measure of the percentage of saturation with carboxyhemoglobin. Hartridge has calibrated his instrument for various degrees of saturation with carbon monoxid by cross-checking in the same sample the amount of saturation by pumping out the carbon monoxid with the aid of ferricyanid and determining the amount present by chemical analysis. In this manner the spectroscopic method has shown very close agreement (2 per cent.) with the percentage saturation as shown by actual analysis. On using this method Hartridge was unable to find evidence of oxygen secretion either during rest, when there was breathing under conditions of diminished oxygen supply, or during moderate exercise. More recently Barcroft further investigated this problem by the direct method, making actual determinations of the oxygen tension of the arterial blood from samples drawn directly from the radial artery of the human body, while both at rest and performing work under conditions of oxygen want. In this experiment, Barcroft exposed himself for a period of six days to a low oxygen tension in a closed chamber large enough to contain him comfortably. After a certain degree of acclimatization was presumably produced, so as to give an opportunity for any secretory action of the pulmonary epithelium to be called into play, the radial artery was exposed in his wrist, a cannula inserted

and a sample was withdrawn. At the same time samples of the alveolar air were obtained. Other samples were drawn after he had performed a certain amount of work on a bicycle ergometer. Under these conditions, Barcroft's arterial blood showed no greater saturation with oxygen than would be expected from the actual tension of the oxygen present in the alveolar air, and the expected saturation at that tension as shown by the dissociation curve of Barcroft's blood. In this connection it should be stated that Haldane and his co-workers believed that the ability to secrete oxygen on the part of the lungs is a function which may be readily lost by persons who are in poor condition, and that one reason why certain individuals fail to adapt themselves to high altitudes is that this faculty of oxygen secretion fails to develop. On examination of the protocols of the experiment, it will be seen that Barcroft felt by no means well during the course of the experiment, and the absence of oxygen secretion as shown by this experiment might be laid to the fact that he failed to adapt himself fully to the lowered tension of oxygen. The procedure of obtaining blood samples in this case by the surgical exposure of the radial artery and by the placing of a cannula therein was doubtless of a heroic order and such experiments are not likely to be often repeated. However, Stadie has shown that samples of arterial blood may be drawn from large arteries when suitable precautions are employed, by the use of a hypodermic syringe in fashion similar to that used in obtaining samples of venous blood. Consequently, it will be seen that the question of oxygen secretion by the pulmonary epithelium may be further investigated by direct methods.

While, therefore, the evidence brought forward by Hartridge and very convincingly by Barcroft would show that there is no secretion of oxygen by the pulmonary epithelium, nevertheless, the result obtained by Douglas, Haldane, Henderson and Schneider on Pike's Peak must be regarded as inexplicable on any other theory. Again, the case of the Duc d'Abruzzi and his companions who successfully lived for a considerable period of time on the Himalayas at an altitude exceeding 24,000 feet and who, while living at this altitude, were able to do a considerable amount of muscular work in the way of climbing without special discomfort, could not be explained on any other grounds than that the tension of oxygen in the blood must have been considerably higher than that in the alveolar air. At this great altitude the pressure of the oxygen in the alveolar air could not have exceeded 30 mm. The work of those who have investigated the dissociation curve of normal individuals shows that at this tension the hemoglobin would be only 50 per cent. saturated with oxygen, even if we assume that there was no loss of tension in the process of diffusion through the alveolar epithelium. Admitting a 5 mm. loss, which seems reasonable, then the hemoglobin could not be more than 40 per cent. saturated. In fact, without some special means for raising the oxygen tension of the arterial blood, the whole body must have been in that state of oxygen want which renders experimental animals entirely inefficient

and often causes them to succumb. Yet in the accounts of d'Abruzzi and his companions as to their gradual ascent from a level of about 17,000 feet to the great altitude of 24,000 feet, which far exceeds that at which any human being had theretofore lived and worked, we find no reference made to any special discomfort caused by mountain sickness and indeed their symptoms were so unnoticeable that Dr. Filipo d'Filippi in his interesting account of this expedition states "the fact of the immunity admits of but one interpretation,—rarification of the air under ordinary conditions of the high mountains, to the limits reached by man at the present date (12 9/32 inches) does not produce mountain sickness." It should be noted though in this connection that d'Abruzzi and his companions reached this altitude very gradually, beginning with an altitude of 17,000 feet, that two months or so were passed in attaining their highest altitude and that therefore the fullest opportunity was given to the members of the party to become thoroughly acclimatized. Moreover, the regular exercise and outdoor life incident to the expedition must have placed them in prime physical condition before they began their ascent. We may therefore suppose that the fullest possible adaptation to life at low oxygen tension took place in the case of the members of this expedition.

The studies made by the Army in connection with the Air Service show that so long as adaptation to low oxygen tension is at all practicable the body makes this adaptation, and the subject is not conscious of any symptoms of the adaptive strain under which the body is laboring, until the point is reached at which compensation is no longer practicable and breakdown occurs. We have seen how in the case of the fatal ascension of Tissandier and his companions that they failed to realize their dangerous position until they were so overcome by the effects of oxygen want that they were unable to make use of the supply of oxygen provided by Paul Bert's forethought which stood ready for their use, and which alone could have averted the catastrophe. While, therefore, the Duc d'Abruzzi and his companions successfully invaded these lofty regions, there is a certain internal evidence that the high altitude was not without its effect upon them, for we learn that they suffered decrease in appetite and consequently loss of strength through lack of nourishment. This would indicate that there is a limit to the completeness with which men may adapt themselves to high altitudes, and that in the case of this expedition the limit of adaptation was, without other special means of assistance, in all probability very nearly reached.

So much then for the status of the theory of oxygen secretion by the epithelium of the lungs upon which, in the opinion of the author, further work must be done before the question may be considered as fully settled.

CHANGES IN THE ACID-ALKALI BALANCE OF THE BLOOD.—Finally, there remains for discussion the effects of exposure to diminished barometric pressure upon the acid-alkali balance of the body and the manner

in which changes in this balance are reflected by the dissociation curve of hemoglobin for oxygen. We have seen that this curve, as shown in Chart 4, is an S-shaped curve with a form varying more or less in different individuals in accordance with what Barcroft calls the pleonectic, mesectic and mionectic form of the curve. Since the regular effect of ascending to a high altitude is to diminish the tension of the carbon dioxide present in the alveolar air, and consequently in the blood, in the absence of any other compensatory change, the deficit in carbon dioxide would lower the hydrogen-ion concentration of the blood and hence render it more alkaline. This would increase the affinity of hemoglobin for oxygen and we would expect that the dissociation curve of the individual's blood would be found displaced to the left upon ascending to a high altitude. Yet much modification of the affinity of the blood for oxygen brought about by lowered hydrogen-ion concentration would by no means be advantageous, for though the affinity for oxygen is increased, the hemoglobin parts with oxygen to the tissues much less readily. Moreover, since the respiratory center is stimulated by increases in the hydrogen-ion concentration, the diminished acidity of the blood would fail to stimulate the respiratory center to a degree of activity commensurate with the oxygen demands. Indeed, it is well known that by forced breathing the carbon dioxide may be washed out of the blood and its hydrogen-ion concentration lowered thereby to such an extent that apnea results and dangerous symptoms of oxygen want may supervene without any respiratory efforts being made by the subject of the experiment. The observations of Barcroft and others have shown us that change in the dissociation curve due to the carbon dioxide deficit does not take place on ascending to a high altitude. Consequently, the loss in acid caused by diminished tension of carbon dioxide has been replaced by other acid substances.

It has been shown by Barcroft that on the performance of muscular work the dissociation curve is affected by the lactic acid present in the blood so that it becomes displaced to the right, in other words the individual changes from the mesectic type to the mionectic type. This change is in the interest of the easy supply of oxygen to the tissues, for while it is true that blood does not become saturated with oxygen in the lungs to the former extent, on the other hand it parts with its oxygen to the tissues with much greater facility and the slight loss in degree of saturation from the lungs is more than made up for by the increased rapidity in the circulation. In muscular work at high altitudes the same effect is evident. Barcroft contrasts his generally depressed and let-down condition during the experiments at Teneriffe with his much greater feeling of comfort on Col d'Olen, and attributes the differences observed at similar altitudes to the fact that he reached his destination at Teneriffe on mule back, while on Col d'Olen the station was reached on foot. The result of the muscular exercise was to increase the hydrogen-ion concentration of his blood through the lactic acid produced, and hence render his blood disso-

ciation curve mionectic. While the performance of muscular work, as in climbing a mountain, may diminish the effects of mountain sickness by the lactic acid produced, it must not be supposed, however, that the increase in hydrogen-ion concentration of the blood which is an effect of acclimatization to high altitudes is produced by lactic acid. The determination of lactic acid in the blood by Ryfel's delicate method has shown no increase in the lactic acid present in the blood in the resting individual at high altitude, although there must have been a definite increase in other acid substances in order to make up for the deficit in carbon dioxide, since the dissociation curve remained unchanged. Moreover, the mionectic condition produced by lactic acid consequent on exercise is but a temporary condition and passes off after a few hours' rest, for lactic acid is readily excreted by the kidneys. On the other hand, the increase in hydrogen-ion concentration of the blood caused by sojourn in high altitudes, is a much more persistent condition, and will remain for some time after the individual has gone down again to a lower level.

We have seen that the general equation for the blood dissociation curve is expressed by the formula

$$\frac{y}{100} = \frac{kx^n}{1 + kx^n}$$

Since n remains practically constant with an approximate value of 2.5, the transition of the blood from a pleonectic or mesectic to a mionectic form of curve will be reflected in changes in the constant k , which becomes steadily smaller as the hydrogen-ion concentration of the blood increases. The change in the hydrogen-ion concentration of the blood is probably one of the important processes of adaptation by which acclimatization to high altitudes is effected. Further studies in the general problem of the acid-alkali balance of the blood will undoubtedly throw some light upon this process of adaptation. It will be proper here to say a few words concerning the effect of muscular exercise upon this constant k . It has been found that muscular exercise both at sea level and at high altitudes caused reduction in the value of this constant in similar fashion. Thus Barcroft gives the following variations in this constant in which parallel climbs of 1,000 feet in elevation each are contrasted: at Carlingford, starting from sea level to 1,000 feet altitude, and at Col d'Olen, climbing from 9,000 to 10,000 feet.

VALUES OF k (ROBERTS)

	CARLINGFORD 1000 feet in 20 minutes.	COL D'OLEN 1000 feet in 33 minutes.
Before start	0.00033	0.00033
At finish	0.00018	0.00016
Change in k	0.00015	0.00017

In this table we see that the constant k has decreased in value by more than 100 per cent.

To quote Barcroft the physiological significance of the mionexy and of the acidosis is as follows:

"The essence of any mechanism of adaptation to high altitudes must be a 'speeding-up' of the whole process of respiration, physical and chemical. The blood in the lung is exposed to a lower oxygen pressure than usual; it is saturated to a less extent with oxygen than formerly. The tissues begin to suffer from oxygen want: a very trifling change in the blood is enough to produce a great change in the circulatory conditions; the pulse quickens, respiration becomes deeper and more rapid, the amount of blood which leaves the lung increases perhaps twofold. Let the reader picture to himself each corpuscle as a ship with its little cargo of oxygen and twice as many of these are leaving the lung as before; they go to the tissue and go through the capillary at perhaps twice their former velocity: but stay—how are they to unload their cargo in the reduced time at their disposal? How futile would be the whole scheme if the corpuscle bolted through the capillary carrying its oxygen into the vein with it. Here is the advantage of mionexy. The mionectic blood parts with its oxygen with much greater rapidity than does the normal blood under given circumstances. Therefore when the corpuscle gets to the capillary it can discharge its cargo with unusual facility."

Barcroft points out that while climbing to reach an altitude, the degree of acidosis actually present is greater than that shown by the dissociation curve, for the hydrogen-ion concentration of the blood is being increased in a twofold manner; first, by the acid substances produced to make up for the deficit in carbon dioxid lost through the diminished tension of carbon dioxid in the blood, and second, through the lactic acid produced by exercise. The natural effect of these conditions is to cause the blood to be slightly more acid than formerly for while it is much poorer in carbon dioxid, it is much richer in other acids than before. This diminished amount of carbon dioxid in the blood reduces the percentage of carbon dioxid in the alveolar air and therefore raises the oxygen pressure in the alveolar air higher than otherwise would be the case. This increase in the oxygen tension of the alveolar air raises the rate at which blood can acquire oxygen and at the same time increases the degree of saturation, so that the lessened combining power of the blood with oxygen caused by the mionexy is more than offset by the increased tension of oxygen in the alveolar air, while very great advantage from this condition is gained by the increased facility with which the blood gives up its oxygen to the tissues.

Prevention of Mountain Sickness.—We have seen that there are wide limits in the tolerance of different individuals for diminished barometric pressure. Physical fitness, rich blood, a good cardiovascular system, nerve-centers which are sensitive to oxygen want, and ability of the blood to change its hydrogen-ion concentration to suit the conditions, seem to constitute the factors which enable one most readily to

adapt himself to diminished barometric pressure. It is perhaps for this reason that we hear so little of the effects of mountain sickness from people who are fond of mountain climbing, for by the constant physical exercise involved the organism has been placed in the best condition to adapt itself to the fullest possible extent to changes in barometric pressure. It is for these reasons too that we divine how it is that persons out of condition, or suffering from cardiac defects or from anemia find great difficulty in adjusting themselves to diminished barometric pressure and are often unable to live even at moderate elevations. One must consider that even in the resting condition at a high altitude one is already partly out of breath, so that the oxygen required by any added muscular exercise must be provided by a body already working on a high plane of effort. Where great heights are attained in a passive way, as undoubtedly will be more frequently the case as the commercial use of the aeroplane develops, there can be no question of any process of acclimatization, as the exposures to diminished barometric pressure are not sufficiently long for any genuine acclimatization to become possible. Whatever adaptation is made must be accomplished by the emergency adaptive mechanism of the body. Observations made on aviators during the war showed no evidence of any real acclimatization even in aviators who frequently patrolled at great heights. On the contrary, they showed that accidents, mistakes in judgment, inefficiency, loss of memory of facts observed during patrols, sleeplessness and general decline in physical fitness made their appearance in aviators as a result of frequent flights at high altitudes which at first were borne without particular disturbance by the individual. Yet the conditions of aviation are such as to make it imperative for all engaged therein to maintain the fullest possible measure of physical and mental efficiency at all times. Fortunately the symptoms due to diminished barometric pressure may be abolished at any time by inhalations of oxygen gas. Such inhalations should be administered by properly devised apparatus through a properly fitting mask, and to be effective should be commenced before actual symptoms have made their appearance. The apparatus devised by Dreyer seems to be effective in this connection. It is designed to be continuously worn and the oxygen supply is regulated by aneroid adjustment so that the amount of oxygen supplied is increased as the barometric pressure diminishes. The importance of some such apparatus as this for the administration of oxygen when flying at high altitudes is all the greater because the aviator himself is rarely conscious of the extent to which his faculties have been benumbed by oxygen want. It is only upon inhalation of oxygen that he becomes conscious of the degree to which his faculties have been impaired. Thus the roar of the motor, which through dulling of the hearing, had been reduced to a faint hum, is perceived to its full extent. Sky which has appeared black, again becomes a brilliant blue. All the faculties are revived to their normal vigor. The body once more recovers its former poise and certainty of action; mus-

cular movements, which formerly appeared to require a gigantic effort, become ridiculously easy in contrast. Besides this, the headache, the extreme fatigue, the benumbed and dazed mental condition frequently observed on landing after flights at great altitudes, as well as the poor appetite fail to make their appearance, when oxygen inhalations are practised. For those who desire to indulge in mountain climbing or to live at high altitudes, attention to the laws of hygiene in placing the body in the best physical condition by means of suitable diet and exercise forms the best preliminary training. Where the contemplated sojourn is long and the altitude is high, the process of acclimatization will be furthered by a gradual ascent to the proposed level, sojourns of several days each at lower levels being undertaken.

BIBLIOGRAPHY

Conditions Due to Compressed Air

- BABINGTON and CUTHBERT. Paralysis caused by working under compressed air in sinking the foundations of Londonderry New Bridge. Dublin Quart. Jour. Med. Sci., 1863, xxxvi, 312-318.
- BASSOE, P. The late manifestations of compressed air disease. Am. Jour. Med. Sci., Phila. and New York, 1913, clxv, 526-542.
- Tr. XV Inter. Cong. Hyg. and Demogr., Wash. (1912), 1913, iii, 626-638.
- BERT, P. La pression barométrique, recherches de physiologie expérimentale. Paris, 1878, G. Masson.
- BLANCHARD et REGNARD. Sur les accidents de la décompression chez les animaux. Soc. biol.; Gaz. med. de Paris, 1881, No. 21.
- BOOT, G. W. Caisson workers' deafness. Ann. Otol., Rhinol. and Laryngol., St. Louis, 1913, xxii, 1121-1132.
- BORNSTEIN, A. Ueber den Einfluss der comprimierten Luft auf die Blutbildung. Arch. f. d. ges. Physiol., Bonn, 1911, cxxxviii, 609-616.
- Versuche über die Prophylaxe der Pressluftkrankheit. Berl. klin. Wehnschr., 1910, xlvii, 1272-75.
- Physiologie und Pathologie des Lebens in verdichteter Luft. Berl. klin. Wehnschr., 1914, li, 923-928.
- Erfahrungen über Pressluftkrankheit. Vierteljahrschr. f. gerichtl. Med., Berlin, 1912, n. F. xlv, 357-375.
- BORNSTEIN und PLATE. Ueber chronische Gelenkveränderungen entstanden durch Presslufterkrankung. Fortschr. a. d. Geb. d. Röntgenstrahlen, Hamburg, 1911-1912, xviii, 197-206.
- BOYCOTT, A. E. Caisson disease. Quart. Jour. Med., Oxford, 1907-8, i, 348-375.
- BOYCOTT and DAMANT, G. C. C. On the blood volume of goats and its relation to their varying susceptibility to symptoms of caisson disease. Proc. Physiol. Soc. Lond., 1907, xiv.
- Some lesions of the spinal cord produced by experimental caisson disease. Jour. Path. and Bact., Cambridge, 1907-8, xii, 507-515, 2 pl.
- Experiments on the influence of fatness on susceptibility to caisson disease. Jour. Hyg., Cambridge, 1908, viii, 445-456.
- BOYCOTT, A. E., DAMANT, G. C. C., and HALDANE, J. S. The prevention of compressed air illness. Jour. Hyg., Cambridge, 1908, viii, 324, 443, 3 pl.
- BRAND, J. D. Over ongevallen bij pneumatische funderingen. Nederl. Tijdschr. v. Geneesk., Amsterdam, 1905, ii, xli, No. 2, Part 2, 34-40.

444 MORBID CONDITIONS DUE TO BAROMETRIC PRESSURE

- BRIZE-FRADIN. *La chimie pneumatique appliquée aux travaux sous l'eau*. Paris, 1808.
- BROOKS, H. An experimental study of caisson disease. *Proc. New York Path. Soc.*, 1907-8, vii, 58-87.
- BUCQUOY. *Actions de l'air comprimé sur l'économie humaine*. Strasbourg, 1861.
- CASSAET. *Des accidents de l'entrée de l'air dans les veines comparés à ceux des ouvriers tubistes*. Bordeaux, 1889.
- . *De la pathogénie des accidents de l'air comprimé*. Thèse de Bordeaux, 1886.
- CATSARAS. *Recherches cliniques et expérimentales sur les accidents survenant par l'emploi des scaphandres*. *Arch. de Neurol.*, Paris, 1890, xix, 48-77; Paris, 1890, 328 p., 5 tab. 8°.
- CITROEN, S. *Over het ontstaan van caisson ziekte*. *Nederl. Tijdschr. v. Geneesk.*, Amsterdam, 1908, i, 1916-1924.
- CLARK, E. A. Effects of increased atmospheric pressure upon the human body; with a report of thirty-five cases brought to the City Hospital from the caisson of the St. Louis and Illinois Bridge. *Med. Arch.*, St. Louis, 1870-1871, v, 1. (*Also reprint of paper.*)
- . *Diving manual*, by authority of the Lords Commissioners of the Admiralty. London, 1907, li, 111. V. Schr.
- ERDMAN, S. The acute effects of caisson disease or aeropathy. *Am. Jour. Med. Sci.*, New York and Phila., 1913, clxv, 520-26; *Ibid.*, Tr. XV Internat. Cong. Hyg. and Demogr., Wash. (1912), 1913, iii, 619-25.
- FERRANNINI, L. *Le alterazioni del sangue per affetto delle variazioni della pressione atmosferica*. *Riforma med.*, Napoli, 1914, xxx, 182-186.
- FOLEY, A. E. *Du travail dans l'air comprimé; étude médicale, hygienique et biologique faite au Pont d'Argenteuil*. Paris, 1863.
- FRENCH, G. R. W. *Observations on deep sea diving*. *U. S. Nav. Med. Bull.*, Wash., 1915, ix, 227-253.
- GREENWOOD, M. The effects of rapid decompression on larvæ. *Jour. Physiol.*, Cambridge, 1906, xxxv.
- . The influence of increased barometric pressure upon man; saturation of the tissue fluids with nitrogen. *Brit. Med. Jour.*, Lond., 1907, i, 373.
- GREENWOOD, M., Jr. Arris and Gale lectures on the physiological and pathological effects which follow exposure to compressed air. *Brit. Med. Jour.*, Lond., 1908, i, 914; 983.
- GUERARD. *Note sur les effets physiologiques et pathologiques de l'air comprimé*. *Ann. d'hyg. pub. et de med. leg.*, Paris, 1884, 2 serie, Tome i, pp. 279-304.
- HALDANE, J. S. *Work under pressure and in great heat*. *Science Progr.* 20th Cent., Lond., 1907-8, ii, 378-398.
- . Some recent investigations in the hygiene of subterranean and sub-aqueous work. *Trans. XIV Internat. Cong. Hyg. and Demogr.*, Berlin, 1907.
- HALLEY, E. *The art of living under water*. *Transactions angl. (Cloche de Halley)*, *Philosophical transactions*, 1716, xxix. and xxxi.
- HAM, C., and HILL, L. E. Effect of increased carbon dioxide tension, together with increased atmospheric pressure. *Proc. Physiol. Soc. Lond.*, 1905, p. 7.
- . Estimation of the gas set free in the body after rapid decompression from high atmospheric pressure. *Proc. Physiol. Soc. Lond.*, 1905, p. 5; *Ibid.*, 1905, July 1, p. 6.
- . Oxygen inhalation as a means to prevent caisson and diver's sickness. *Proc. Physiol. Soc. Lond.*, 1905, p. 6.
- HELLER, R. *Die Caissonkrankheit; eine Monographie*. Zurich, 1912, Leemann & Co.
- HELLER, R., MAGER, W., and SCHROETTER, H. V. *Luftdruckerkrankungen*. Wien, 1900.
- HERSENT, H. *Travaux publics*. Paris, 1889, Imprim. Chaix.
- . *Note sur l'emploi de l'air comprimé pour l'exécution des ouvrages*

- hydrauliques et spécialement des fondations. Expériences faites à Bordeaux. Paris, 1895, Chaix.
- HILL, L. E. Caisson sickness. Edward Arnold, London, 1912.
- The physiology of submarine work. Rep. Brit. Assn. Adv. Sc., 1911, London, 1912, 634-647.
- HILL, L. E., and MACLEOD, J. J. R. Caisson illness and diver's palsy. An experimental study. Jour. Hyg., Cambridge, 1903, iii, 401-445.
- The influence of compressed air on the respiratory exchange. *Ibid.*, 493.
- The influence of compressed air and oxygen upon the gases of the blood. Jour. Physiol., 1903, xxix, 382.
- HILL, L., and GREENWOOD, M., Jr. The influence of increased barometric pressure on man. Proc. Roy. Soc. Lond., 1907, Series B, lxxix, 21-27.
- The influence of increased barometric pressure on man. No. III. The possibility of oxygen bubbles being set free in the body. Proc. Roy. Soc. Lond., 1907, Series B, lxxix, 284-287.
- The influence of increased barometric pressure on man. No. IV. The relation of age and body weight to decompression effects. Proc. Roy. Soc. Lond., 1908, Series B, lxxx, 12-24.
- The influence of increased barometric pressure upon man. Proc. Roy. Soc. Lond., 1905-6, Series B, lxxvii, 442-453.
- On the formation of bubbles in the vessels of animals submitted to a partial vacuum. Jour. Physiol., Lond., 1910, xxxix, 23.
- HOPPE, F. Ueber den Einfluss, welchen der Wechsel des Luftdruckes auf das Blut ausübt. Arch. f. Anat., Physiol. u. wissenschaft. Med., Leipzig, 1857, xxiv, 63-73.
- JAMINET, A. Physical effects of compressed air, and of the causes of pathological symptoms produced on man, by increased atmospheric pressure employed for the sinking of piers, in the construction of the Illinois and St. Louis Bridge over the Mississippi River at St. Louis, Missouri. St. Louis, Mo., 1871.
- JAPP, H. Caisson disease and its prevention. Tran. XV Inter. Cong. Hyg. and Demogr., Wash. (1912), 1913, iii, 639-654.
- JOURDANET, D. Influence de la pression de l'air sur la vie de l'homme. Paris, 1876.
- KEAYS, F. L. Compressed air illness. New York, 1909.
- LEPINE, J. Sur les lésions médullaires de la décompression brusque. Bull. Soc. de biol., Paris, Oct. 27, 1900.
- LEROY de MERICOURT. Consideration sur l'hygiène des pêcheurs d'éponges. Ann. d'Hyg. pub. et de med. leg., Seconde Série, 1869, xxxi, 274-286.
- MOWHORTER, J. E. The etiological factors of compressed air illness; the gaseous contents of subaqueous tunnels; the occurrence of the disease in workers. Am. Jour. Med. Sci., Phila. and New York, 1910, cxxxix, 373-383.
- MACNAUGHTON, G. W. F. Frictional electricity, a factor in caisson disease. Lancet, London, 1906, ii, 435.
- MUSENGA, G. Un pescatore de spugna (sommizzatore) che senza apparecchio si tuffa fino a 80 metri. Ann. de med. nav., Roma, 1915, i, 163-167.
- OLIVER, Sir T. An address on the physiology and pathology of work in compressed air. Brit. Med. Jour., London, 1909, i, 257-261.
- PANUM. Untersuchungen über die physiologischen Wirkungen der comprimierten Luft. Pflüger's Archiv f. Physiol., Bonn, 1868, i, 125-165.
- PHILIPPON, G. Action de l'oxygène et de l'air comprimé sur les animaux a sang chaud. Compt. rend. de l'Acad. des Sciences de Paris, 1893, cxvi.
- Effets de la décompression brusque sur les animaux placés dans l'air comprimé. Compt. rend. de l'Acad. des Sciences de Paris, 1892, cxv, 186-188.
- Effets produits sur les animaux par la compression et la décompression. Jour. de l'anat. et de physiol. norm. et pathol. de l'homme et des animaux, Publié par Duval, 1894, Nos. 3 et 4; 1895, No. 4.

- PLESCH, J. Zur Prophylaxie und Therapie der Caissonkrankheit. *Verhandl. d. deutsch. Kongr. f. innere med.*, Wiesbaden, 1910, xxvii, 254-263.
- POL and WATELLE. Mémoire sur les effets de la compression de l'air appliqués au creusement des puits à houille. *Ann. d'hyg. pub. et de méd. lég.*, Seconde Série, 1854, i, 241-279.
- REGNARD, P. La vie dans les eaux. Paris, 1891, G. Masson. V. Schr.
- Recherches expérimentales sur les conditions physiques de la vie dans les eaux. Paris, 1891, G. Masson.
- Recherches expérimentales sur l'influence des très hautes pressions sur les organismes vivants. *Compt. rend. de l'Acad. des Sciences de Paris*, xcvi, 745-747.
- v. RENSELLAER. Pathology of caisson disease. *New York Med. Record*, 1891, xl, 141, 175.
- Transactions of Med. Soc., New York and Phila., 1891, pp. 144-408.
- Report of the Admiralty Committee on deep diving. Blue Book, London, 1907.
- v. SCHROETTER. Der Sauerstoff in der Prophylaxie und Therapie der Luftdruck-erkrankungen. Berl., 1906, A. Hirschwald.
- v. SCHROETTER, H., HELLER, R., und MAGER, W. Zur Kenntniss der Todesursache von Pressluftarbeitern. *Deutsche med. Wchnschr.*, 1897, Nr. 24, ff.
- Experimentelle Untersuchungen über die Wirkung rascher Veränderungen des Luftdruckes auf den Organismus. *Archiv. für die ges. Physiol.*, 1897, lxxvii, 1-116.
- Bemerkungen zu dem Aufsätze des Herrn Hofrath Dr. G. v. Liebig: "Warum man unter einem stark erhöhten Luftdrucke sowohl wie unter einem stark verminderten nicht mehr pfeifen kann." *Munch. med. Wchnschr.*, 1897, Nr. 14.
- SILBERSTERN, P. Die Gefahren der Caissonarbeit. *Tr. XV Internat. Cong. Hyg. and Demogr.*, Wash. (1912), 1913, iii, 610-619.
- SMITH, A. H. The physiological, pathological, and therapeutical effects of compressed air. Detroit, 1886. (A second edition of "The Effects of High Atmospheric Pressure, including the Caisson Disease," 1873.)
- SMITH, J. L. The pathological effects due to increase of oxygen tension in the air breathed. *Jour. Physiol.*, 1899, xxiv, 19.
- SNELL, E. H. Compressed air illness. London, 1896.
- THOMSON, T. K. An unsuspected cause of caisson disease. *Tr. XV Internat. Cong. Hyg. and Demogr.*, Wash. (1912), 1913, iii, 608-10.
- TRIGER. Mémoire sur un appareil et autres travaux, sous les eaux et dans les sables submergés. *Compt. rend. de l'Acad. des Sci.*, 1841, xiii, 884-896.
- TWORT, J. F., and HILL, L. Further experiments on the effect of breathing oxygen on the nitrogen dissolved in the urine. *Proc. Physiol. Soc. Lond.*, 1911-12, 42-4.
- Compressed air illness. I. Solubility of compressed air in water and oil. *Proc. Physiol. Soc. Lond.*, 1910, xli, 5.
- TWORT, J. F., WALTER, H. B., and HILL, L. Compressed air illness. II. The desaturation of the arterial blood as measured by the nitrogen dissolved in the urine. *Proc. Physiol. Soc. Lond.*, 1910, xli, 6.
- VERNON, H. M. The solubility of air in fats and its relation to caisson disease. *Lancet*, London, 1907, ii, 691-693.
- The solubility of air in fats and its relation to caisson disease. *Proc. Roy. Soc. Lond.*, 1907, Series B, lxxix, 366-371.

Conditions Due to Diminished Barometric Pressure

- Air Service, Medical, War Department, Division of Military Aeronautics, Washington, D. C., 1919.
- BARCROFT, J. The respiratory function of the blood. Cambridge, 1914.
- Anoxemia. *Lancet*, London, Sept. 4, 1920, ccxix, No. 10, p. 485.

- BARCROFT, J., COOK, A., HARTRIDGE, H., PARSONS, T. R., and PARSONS, W.** Flow of oxygen through pulmonary epithelium. *Jour. Physiol., Cambridge*, 1920, liii, 450.
- BERT, P.** *La Pression Barométrique.* Paris, 1878.
- BIRLEY, J. L.** Principles of medical science as applied to military aviation. *Lancet*, London, 1920, exxviii, Nos. 5048, 5049, 5050, pp. 1147, 1205, 1251.
- CHRISTIANSEN, J., DOUGLAS, C. G., and HALDANE, J. S.** The dissociation of O₂ from human blood. *Jour. Physiol., London*, 1913, xlvii, 2.
- The absorption and dissociation of carbon dioxide by human blood. *Jour. Physiol., London*, 1914, xlviii, 244-271.
- DOUGLAS, C. G., HALDANE, J. S., HENDERSON, Y., and SCHNEIDER, E. C.** Physiological observations made on Pike's Peak, Colorado, with special reference to adaptation to low barometric pressures. *Phil. Trans. Roy. Soc. London*, 1913, Series B, cciii, 185 et seq.
- DOUGLAS, C. G., HALDANE, J. S., and HALDANE, J. B. S.** The laws of combination of hemoglobin with carbon monoxide and oxygen. *Jour. Physiol., Cambridge*, 1912, xli, 275.
- DOUGLAS, C. G., and HALDANE, J. S.** The causes of absorption of oxygen by the lungs. *Jour. Physiol., Cambridge*, 1912, xli, 305.
- ELLIS, M. M.** Respiratory volumes of men during short exposures to constant low oxygen tensions attained by rebreathing. *Am. Jour. Physiol., Baltimore*, 1919-20, i, 267.
- GREGG, H. W., LUTZ, B. R., and SCHNEIDER, E. C.** Compensatory reactions to low oxygen. *Amer. Jour. Physiol., Baltimore*, 1919-20, i, 302.
- The changes in the content of hemoglobin and erythrocytes of the blood in man during short exposures to low oxygen. *Amer. Jour. Physiol., Baltimore*, 1919-20, i, 216.
- HALDANE, J. S.** Symptoms, causes and prevention of anoxemia. *Brit. Med. Jour., London*, 1919, No. 3055, p. 65.
- HARTRIDGE, H.** A spectroscopic method of estimating carbon monoxide. *Jour. Physiol., Cambridge*, 1912, xli, 1-20.
- The action of the various conditions on carbon monoxide hemoglobin. *Jour. Physiol., Cambridge*, 1912, xli, 22-33.
- KROGH, A., and KROGH, M.** On the tensions of gases in the arterial blood. *Skand. Arch. f. Physiol.*, 1910, xxiii, 179.
- On the combination of hemoglobin with mixtures of oxygen and carbonic oxide. *Skand. Arch. f. Physiol.*, 1910, xxiii, 217.
- Some experiments on the invasion of oxygen and carbonic oxide into water. *Skand. Arch. f. Physiol.*, 1910, xxiii, 224.
- On the mechanism of gas exchange in the lungs. *Skand. Arch. f. Physiol.*, 1910, xxiii, 235.
- On the rate of diffusion of carbonic oxide into the lungs of man. *Skand. Arch. f. Physiol.*, 1910, xxiii, 236.
- LUTZ, B. R., and SCHNEIDER, E. C.** The reactions of the cardiac and respiratory centers to changes in oxygen tension. *Amer. Jour. Physiol., Baltimore*, 1919-20, i, 327.
- PETERS, R. A.** Chemical nature of specific oxygen capacity in hemoglobin. *Jour. Physiol., Cambridge*, 1912, xli, 131.
- RAVENHILL, T. H.** Some experiences with mountain sickness in the Andes. *Jour. Trop. Med. and Hyg.*, London, 1912, xl, 313.
- STADIE, W. C.** The oxygen of the arterial and venous blood, etc. *Jour. Exper. Med.*, New York, 1919, xxx, No. 3, p. 225.
- v. TSCHUDI.** Peru, Reiseskizzen aus den Jahren 1838-1842, ii, Saint Gallen, 1846.
- ZUNTZ, LOEWY, MÜLLER, and CASPARI.** Höhenklima und Bergwanderungen in ihrer Wirkung, etc. Berlin, 1906.

SECTION VI

DISEASES OF THE BONES AND JOINTS

CHAPTER I

DISEASES OF THE BONES AND JOINTS

BY ROBERT SOUTTER, M.D., F.A.C.S.

Diseases of the bones, p. 450:—Fractures, p. 450:—Fracture of the spine, p. 450; Fracture of the neck of the femur, p. 451; Fracture of the metatarsal bones, p. 451; Tibial tubercle injury or separation, p. 451.

Absence of bones, p. 452:—Congenital absence of the long bones—Absence of the fibula, p. 452; Congenital absence or partial absence of other long bones, p. 453; Absence and malformation of vertebræ, p. 454; Absence of ribs, p. 454.

Deformities, p. 455:—Deformity of the thorax, p. 455:—Supernumerary ribs—Absence of ribs, p. 455; Deformity of the chest from rickets, p. 455; Funnel chest, p. 455; Pigeon breast, p. 455—Deformity of the spine, p. 456:—Round shoulders—Stooped shoulders, p. 456; Scoliosis, p. 457; Spina bifida occulta, p. 458—Deformity of the toes, p. 459:—Claw-foot and hammer-toes, p. 459; Deformities of the fingers, p. 460:—Webbed fingers, p. 460; Hypertrophic osteoarthropathy, p. 461; Distorted fingers, p. 461—Other deformities, p. 461:—Congenital elevation of the scapula; Sprengel's deformity, p. 461; Bow-legs and knock-knees, p. 462; Acromegaly, p. 463; Achondroplasia (Chondrodystrophia), Achondroplasia fetalis, p. 465.

Tuberculosis and other diseases of the bones, p. 465:—Tuberculosis of the bones and joints, p. 465; Tuberculosis of the spine (Pott's disease), p. 469; Periostitis, p. 476; Osteomyelitis, p. 477; Typhoid spine, p. 479; Infantile paralysis, p. 479.

Non-infectious paralyses, p. 482:—Cerebral spastic paralysis, p. 482; Spastic spinal paralysis, p. 483; Obstetrical paralysis, p. 484.

Other pathological conditions of the bones, p. 484:—Progressive muscular atrophy, p. 484:—Hand and forearm type (Aran-Duchenne), p. 484; Peroneal type, p. 484; Angel-wing type, p. 485; Large calf type, p. 485; Face and shoulder type (Landouzy-Déjerine), p. 485—Infantile scurvy, p. 485; Congenital torticollis, p. 485; Acquired torticollis, p. 486; Sciatic scoliosis, p. 487; Backstrain, p. 487; Osteogenesis imperfecta—Fragilitas ossium, p. 488; Osteomalacia, p. 488; Osteitis deformans (Paget's disease), p. 489; Painful heel—Bursitis, p. 489; Ingrown toe-nail, p. 490; Hallux rigidus, p. 490; Hallux valgus, p. 490; Hemophilic joint-swelling, p. 491.

Diseases of the joints, p. 492:—Dislocations, p. 492:—Congenital dislocation of the hip, p. 492; Snapping knee, p. 495; Congenital dislocation of the knee, p. 495; Congenital hyperextension of the knee,

- p. 495; Congenital dislocation of the patella, p. 495; Traumatic dislocation of the patella, p. 496; Sacro-iliac injury, p. 496; Subluxation of the clavicle, p. 497; Congenital dislocation of the shoulder, p. 497; Chronic recurrent dislocation of the shoulder, p. 497; Recurrent dislocation of the patella, p. 497; Dislocation of the elbow, p. 498.
- Tuberculosis of the joints, p. 498:—Tuberculosis of the hip, p. 498; Tuberculosis of the knee and ankle, p. 502; Synovial tuberculosis, p. 503; Rice bodies, p. 503; Tuberculosis of the shoulder, p. 503; Tuberculosis of the elbow, wrist and ankle, p. 503.
- Arthritis of the joints, p. 505:—Arthritis, Osteo-arthritis, Arthritis deformans, p. 505; Degenerative or atrophic arthritis, p. 506; Proliferative or hypertrophic osteo-arthritis, p. 507; Infectious arthritis (non-tuberculous), p. 507; Acute arthritis in infancy, p. 508; Gonorrheal arthritis, p. 508.
- Joint deformities, p. 510:—Deformities of the hip, p. 510:—Hip flexion, p. 510; Lordosis, p. 511—Coxa vara, p. 511; Coxa valga, p. 512—Deformity of the knee, p. 513:—Knee flexion, p. 513—Deformities of the ankle and feet, p. 514:—Postural conditions of the feet, p. 514; Equinovarus (club-foot)—Varus, p. 514; Pes cavus, p. 514; Equinus, p. 515; Equinovalgus—Valgus, p. 516; Flat-foot—Valgus, p. 516; Calcaneus—Calcaneovarus—Calcaneovalgus, p. 517; Flail-ankle, p. 517—Deformities of the wrist and hand, p. 518:—Madelung's deformity of the wrist, p. 518; Dupuytren's contraction, p. 518; Congenital club-hand, p. 518.
- Other pathological conditions of the joints, p. 519:—Limited motion and deformity of the arms, p. 519; Ankylosis, p. 520; Semilunar cartilage displacement, p. 521; Prepatellar bursitis, p. 521; Loose bodies in the knee-joint (joint-mice), p. 521; Tenosynovitis, p. 521; Acute synovitis, p. 522; Intermittent synovitis with effusion, p. 522; Charcot's disease, p. 522; Gout, p. 522; Scapula crepitus, p. 523; Sprained ankle, p. 524; Subdeltoid bursitis, p. 525; Ischemic paralysis (contraction), p. 525.

DISEASES OF THE BONES

FRACTURES

Fracture of the Spine.—If there is no immediate crushing of the cord, fracture may simulate disease and may not be differentiated at first, except by the history of trauma. If there is marked crushing of the vertebræ, there may be deformity. The *x*-ray is an aid in diagnosis. Pain and tenderness are usually present, and more or less disability, depending upon the injury. Pressure symptoms develop sooner or later if the spine buckles, or due to congestion following the injury. If the cord is crushed, there will be shock, paralysis, both sensory and motor, below that level, and paralysis of the bladder and rectum. The reflexes may be increased or lost, depending upon the severity of the trauma.

A crushed vertebra or two will sometimes disintegrate progressively so that the symptoms of pressure develop gradually. The deformity will increase as the bone disintegrates.

TREATMENT.—The treatment is by support and **fixation**, or **correction** of the **deformity** by recumbency on a frame, followed by apparatus. A **bone-graft** is often necessary to prevent the recurrence of pressure symptoms, or to prevent the recurrence of deformity after severe fractures or crushing of the vertebrae. The results are very satisfactory. Bone-grafting should be done only by those thoroughly familiar with the technic and with the best methods of asepsis.

The prognosis is good in these cases.

Fracture of the Neck of the Femur (Recent).—**SYMPTOMATOLOGY.**—The symptoms are pain, local tenderness, possibly crepitus and deformity. The pain is often referred to the knee. Usually there is pain in the groin or near the hip-joint if the surgeon strikes the patient's heel with his hand. An *x-ray* plate will show the fracture. There is a history of a fall or of some other injury.

TREATMENT.—The leg should be disturbed as little as possible until all apparatus is ready. Then, under anesthesia, **traction** is applied, and the surgeon **presses** on the **trochanter** until a position of extreme abduction and hyperextension, recommended by Whitman, is reached. The amount of abduction and hyperextension necessary should be determined by trying out the good leg. With the leg in this position, a well-fitting **plaster of Paris bandage** is applied to the thorax, pelvis (including the tuberosity of the ischium), thigh, leg and foot. The patient is placed on a Bradford frame. The leg below the upper third of the femur is unsupported by the bed. The patient may be allowed to use a bed-rest in two weeks—his health will not permit the recumbent position longer than that. This fracture tends to occur in the aged, who cannot endure prolonged recumbency well.

Fracture of the Metatarsal Bones.—**SYMPTOMATOLOGY.**—The symptoms are pain; tenderness and swelling. The pain is not always excessive. Patients may walk for six months or more without treatment. Pain is constantly present to a slight degree, and will persist until the bone is united.

The cause may be very slight. An *x-ray* examination is sometimes necessary for diagnosis.

TREATMENT.—Treatment consists in **immobilization** of the foot and ankle for five weeks by a **plantar splint** and an **ankle and foot plaster**. Walking on the foot is allowed after five weeks, if the bone has united and the swelling has subsided. The plaster must be kept in place when the patient first begins to walk. If the bone does not unite in three months an **operation** will be necessary.

Tibial Tubercle Injury or Separation.—The epiphysis of the tibial tubercle is united about the eighteenth year and may be separated by trauma or by sudden contraction of the extensor muscles of the thigh. There is pain, swelling and local tenderness. In extreme cases there is disability and weakness. An *x-ray* examination will show the separation.

TREATMENT.—Treatment consists in **fixation in extension** long enough to allow the bone to unite. Occasionally an **operation** is necessary to unite the separated bone. The condition is not a serious one.

ABSENCE OF BONES

Congenital Absence of the Long Bones.—Absence of the Fibula.—The absence or partial absence of the fibula or of one of the other long



FIG. 1.—CONGENITAL ABSENCE OF THE FIBULA AND DEFORMITY OF THE FOOT.

bones is not uncommonly seen in an orthopedic clinic. This condition varies from a partial to a total absence of the fibula (Fig. 1). In some instances, only the epiphyseal line, or growing portion of the bone, is affected, without any apparent absence of the bone. In this type of case, the structures of the leg do not grow as they should, and as a result there are deformities in the position of the foot or in the line of the leg.

TREATMENT.—**Operations** are performed to correct the deformity or to supply the bone when absent. In very slight cases an osteotomy of bone is all that is necessary to allow correction of the deformity. In

other cases, the bone must be cut through with an osteotome, the gap separated and filled by an **inlay graft**. The inlay graft is usually preferable to the medullary graft in this type of case. For a total absence of the fibula, a bone-graft may be placed beside the tibia, or a graft may be implanted into the lower tibia and into the tarsal bones to give support to the ankle.



FIG. 2.—CONGENITAL ABSENCE OF METATARSALS AND TOES.

Congenital Absence or Partial Absence of Other Long Bones.—In partial absence of other long bones, the condition is very much the same as in absence of the fibula, and may vary from a defect in the epiphyseal line to a partial or total absence of the bone. When the humerus or the femur are defective, the bones below are often shortened or deformed; but when the bones below are present there is usually some small bone corresponding to the “absent” ones. In the hand or foot any bone may be absent beyond the carpus or tarsus; or it may be affected as above described. If one or more carpal or tarsal bones are

absent, the metacarpal or metatarsal beyond it are apt to be missing (Fig. 2).

Absence and Malformation of Vertebrae.—There may be absence of vertebrae without any additional sign other than an obvious shortness of that part of the spine. Often there is a cleft in the spinal column at the point of deficiency. Supernumerary or deformed vertebrae may



FIG. 3.—SUPERNUMERARY RIB.

cause deformity of the spine; this condition is also one of the causes of congenital scoliosis.

TREATMENT.—The cases should be treated for the scoliosis deformity, the spine straightened as much as possible and the muscles developed to maintain the correction.

Absence of Ribs.—This condition is not uncommon. When it is present there is apt to be unequal, defective formation of the muscles. This may lead to deformity of the spine, and to asymmetry of the thorax.

DEFORMITIES

Deformity of the Thorax

Supernumerary Ribs—Absence of Ribs.—There may be supernumerary ribs or absence of ribs, either in the upper or lower part of the chest. The condition may be unilateral or bilateral. Either a single rib or many ribs may be absent. In some instances, supernumerary ribs cause pain, according to certain authors. In some instances this is due to other causes which would occasion the same pain in the case of patients without cervical ribs. Nevertheless, the pain is often attributed to the supernumerary ribs. If the cervical rib is unilateral, the spine may develop a lateral curvature, as such a rib is often connected with a defective supernumerary vertebra (Fig. 3).

Deformity of the Chest from Rickets.—In rickets, the ribs and cartilages are softer than normal. In breathing, the action of the diaphragm and muscles sucks in the ribs or their cartilages and causes various deformities. In rachitic children the rounding of the soft spine will increase the deformity of the chest. This may cause a symmetrical deformity or an asymmetrical development of the thorax, or a sagging more to one side than to the other. These deformities are due to a soft condition of the bone affecting the growth and development of the chest.

Funnel Chest.—In funnel chest there is a hollow deformity over the various parts of the sternum. Some authors have attributed the condition to a defective ossification or to pressure of the chin on the thorax before birth.

Pigeon Breast.—Pigeon breast is a deformity characterized by an undue prominence of the sternum and of the cartilages of the ribs. This is usually in the median line but may be unilateral.

CAUSATIVE FACTORS.—The cause is usually rickets. There is an increase in the anterior, and a decrease in the lateral diameter.

Deformities of the thorax are also due to a malposition of the spine; or they may be due to asymmetry or lack of development of one or more vertebrae, to disease of the spine, to asymmetry of the pelvis, to a difference in the length of the legs, to asymmetrical development of the muscles, or to disease of the respiratory organs—pneumonia, empyema, pyopneumothorax, etc.

TREATMENT.—Deformities of the thorax are treated by **correction apparatus** on which the patient rests. These are used together with **braces** and **exercises**, to expand the chest. The Clapp crawling exercises are often very useful in this type of deformity. In small children braces should be avoided as much as possible.

Deformity of the Spine

Round Shoulders—Stooped Shoulders.—**ETIOLOGY.**—Round shoulder is a posture of relaxation, weakness and fatigue. Faulty attitudes in standing and sitting are the common causes (Fig. 4). It is to be found also in the case of those who, through occupation or otherwise,



FIG. 4.—FAULTY ATTITUDE IN STANDING. ROUND BACK.

carry heavy loads on their backs. Tight, long garters, and waists that hang from the tip of the shoulders favor round and drooping shoulders (Fig. 5). No less serious as a causative factor is an overheated house, and an indoor life with an atmosphere of indolence, limitation and tension. School life tends to produce round back by its confinement to the desk. The mental element is often of importance.

SYMPTOMATOLOGY.—The most striking symptom is an increase in the dorsal physiological curve. Pain may occasionally be present.

TREATMENT.—Treatment consists of favorable surroundings, **correction of faulty attitude and proper dress.** These may be supplemented by **exercises and apparatus.**

Scoliosis.—**ETIOLOGY.**—Postural scoliosis is due to overloading the spine or to a decreased resistance in growing individuals who sit, stand or work in faulty and onesided postures. Some forms of astigmatism and asymmetrical weakness of the eye-muscle may lead to faulty posture.



FIG. 5.—ROUND SHOULDERS.

Unilateral deafness may also serve to favor the development of scoliosis. The condition may also be caused by empyema, contractures from disease, trauma, defective ribs or vertebrae, difference in the length of the legs, and asymmetrical pelvis (Figs. 6 to 10).

SYMPTOMATOLOGY.—There is an evident, slight or extreme curve in the spine, with or without prominence of the ribs on one side (rotation). Many digestive disturbances and visceral disorders are due to habitual faulty attitudes. In certain cases there may be compression of the thoracic viscera, causing shortness of breath and rapid pulse.

TREATMENT.—Slight cases are improved by corrective **exercises**, light **braces** and corrective **apparatus**. Extreme cases may be improved by gradual or forcible correction in **plaster of Paris**. The physician should adapt the method of treatment to the patient. Delicate children and adults who are sickly should be treated by the gentler corrective methods at first. These consist in braces, developing exercises and gymnastics. Plaster of Paris should be reserved until they are stronger, and, when used, should be supplemented and followed by healthful exercises.

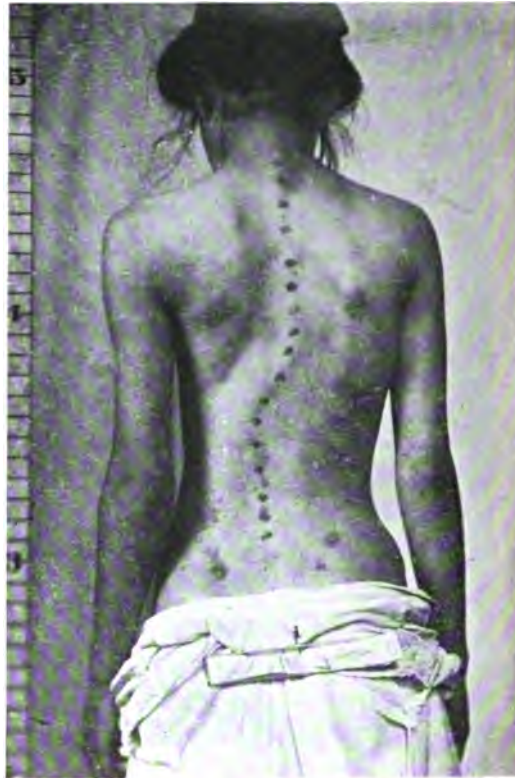


FIG. 6.—SCOLIOSIS, SHOWING A DOUBLE CURVE.

Spina Bifida Occulta.—From the orthopedic point of view, spina bifida is of interest because of the muscular weakness or paralysis and because of the deformity of the spine, which may consist in a postural curve or in an extensive scoliosis with bony changes. There may be club-feet or club-hands, deformed or dislocated hips, subluxated or contracted knees, various malformations, or complete or partial absence of bones. Trophic ulcers are not uncommon. The deformities may be of congenital origin or due to paralysis or static conditions, and there may

be incontinence of feces and urine. Some cases of spina bifida show only a few of the above deformities—in others they are all present.

TREATMENT.—Each deformity will require separate treatment. The muscular weakness will require **muscle-training, exercise and massage.** **Braces** are useful in correcting deformity and as an aid in locomotion. The **tumor**, when not too large, may be left for years untreated and then



FIG. 7.—SCOLIOSIS, SHOWING TOTAL CURVE.

removed, the sac membrane being sometimes inverted, with comparative safety, without being opened.

Deformity of the Toes

Claw-foot and Hammer-toes.—This condition consists in contraction of one or more of the toes. It may be bilateral, and either congenital or acquired. The second phalanx is flexed while the third is extended (Fig. 11).

TREATMENT.—The flexed position of the toes, when slight, may be corrected by **tenotomies** of the capsule and tendons maintaining the deformity. In extreme cases an **operation** on the bone is necessary. The heads of the metatarsals should not be cut or removed. When a bone operation is necessary, it should be on the bone of the phalanx (Fig. 12).

Deformities of the Fingers

Webbed Fingers.—Two or more fingers may be webbed to a varying length by skin, fibrous tissue or even by muscle and bony tissue (Figs.



FIG. 8.—SCOLIOSIS WITH ROTATION.

13 and 14). The thumb is seldom involved. The fingers are sometimes united at their tips in pairs or in a mass.

TREATMENT.—The fingers can usually be separated by a **plastic operation**. The skin from the back of one finger is incised in such a way as to be carried with the second finger, covering its front and side, while the skin from the front of the second finger is incised in such a way that it

is carried away with the first finger when they are separated, and covers its side and back. In this way no granulating area is left.

Hypertrophic Osteo-arthropathy.—This condition usually accompanies preëxisting chronic pulmonary disease. There is marked clubbing of the fingers, overgrowth of the nails, new bone deposit in the metatarsal and metacarpal phalanges and in the distal extremities of the adjoining bones of the arms and legs.



FIG. 9.—SCOLIOSIS. Showing rotation when patient leans forward.

Distorted Fingers.—This condition is congenital, and not uncommon. It should be treated as early as possible by **manipulation, exercise and apparatus**, or by **plastic operations**.

Other Deformities

Congenital Elevation of the Scapula—Sprengel's Deformity.—This condition may affect one or both scapulæ. The scapula is held high

and is usually inclined forward and outward as well as upward and forward. It is less movable than normally on account of the shortening of the muscles and of one or more fibrous or bony bands which attach it to the spine or to the ribs. The position of the scapula causes deformity of the neck and scoliosis or a flat chest anteriorly (Fig. 15).

TREATMENT.—The asymmetry and scoliosis should be treated by stretching and development exercises and gymnastics, braces, etc. Very



FIG. 10.—SCOLIOSIS. Right dorsal, left lumbar curves.

often it is necessary to remove the bands by operation and draw the scapula down to the normal position. The operation should be followed by exercises to overcome the deformities of the spine and chest and to promote the normal mobility of the scapula.

Bow-legs and Knock-knees.—In bow-legs the bowing may be of the femur and tibia or of the tibia alone (Fig. 16). It is a rachitic deformity of children. Knock-knee is an internal prominence of the knee. The bones of the leg form an angle with the femur. The knees are approximated, and the feet are held apart on standing.

TREATMENT.—The deformity is easily corrected by a linear osteotomy at the point of greatest curve, and then the leg is held in a slightly

overcorrected position until locomotion is established. Extreme deformities are very satisfactorily treated in this way. In anterior bowing of the tibia, a small **wedge of bone** is removed instead of a linear osteotomy being performed, which is sufficient elsewhere but not in this case.

When a deformity is due to rickets (Figs. 17 to 19) the bones should **not be operated** upon if the epiphyseal line appears irregular and un-



FIG. 11.—HUMPED FOOT AND CLAW-FOOT.

defined in the *x-ray* plate. If the bones are hard and the patient is three or four years old at least, and the *x-ray* examination shows a clearly defined line, an operation may be advisable. In young children, when the bones are soft, **braces** are usually satisfactory as a means of correcting the deformity, if the curve is near the middle of one of the long bones. In children over five it is better to operate as a brace will accomplish little, and the strain on the joint is sometimes considerable.

Acromegaly.—In acromegaly the jaw, hands and feet or the fingers or toes, or all of these extremities, may enlarge. The changes may be



FIG. 12.—SUPERNUMERARY FOOT.



FIG. 13.—CONGENITAL DEFORMITY OF FINGERS, AND WEBBED FINGERS.

slight and take place slowly over a long period of time, diminishing after the patient is fifty years of age. There is a chronic form with marked enlargement of the head, hands and feet lasting from eight to thirty years. A malignant form is also found which progresses rapidly and lasts about three years. In this form there is general atrophy, cachexia, cardiac disturbance and death. It is supposed to be due to disease of the pituitary gland and analogous to myxedema with disease of the thyroid gland.

Achondroplasia—(Chondrodystrophia)—Achondroplasia Fetalis.—

In this condition the shafts of the long bones of the arms and legs grow small. The end of the bones at the epiphysis grows and broadens. The



FIG. 14.—WEBBED TOES.

wrists, ankles, and knees enlarge and broaden. The body and head grow; the patient is a dwarf with short legs and short arms, and a large head and body (Figs. 20 to 22). The condition differs from rickets in that there is very slight proliferation of cartilage.

Tuberculosis and Other Disease of the Bones

Tuberculosis of the Bones and Joints.—ETIOLOGY.—Tuberculosis of the bones and joints is due to an infection by the tubercle bacillus. The modes of entrance is probably through the mouth, the bronchial glands or the glands of the intestine, and thence to the bone. The disease may occur at any age, but it is most common in children. There is often a history of trauma. The various joints are attacked in the following order of frequency: spine, hip, knee, ankle and elbow.

SYMPTOMATOLOGY.—Tuberculosis of the bones and joints is characterized by atrophy, slow progression of the disease and comparatively

VOL. VI—30.

little pain. At times the pain may be very severe, but in observing the disease over a long period of time pain is not found to be a prominent symptom. Local atrophy is marked. With the x-ray the atrophy of the bone may be noticed.

The limitation of motion at the joint is due at first to spasm, later to the changes about the joint. As these changes improve the joint may become movable again. When there is abscess formation following



FIG. 15.—CONGENITAL ELEVATION OF THE SCAPULA.

tuberculosis of the bone there may be pain due to the tension of the abscess. The pain diminishes as the soft tissues give way and the tension is diminished.

The general symptoms in tuberculosis of the bone come on gradually. The disease has usually progressed for some time before the constitutional symptoms are marked. When the proper treatment is introduced the general symptoms improve markedly. Usually there is an appearance of good general health.

TREATMENT.—In the treatment of tuberculosis, general hygienic measures are very important. Locally the disease should be treated by

rest, immobilization and protection from jar. The efficiency of the treatment may be judged by the local comfort and the general constitutional improvement. The local improvement is gradual.

Operation in tuberculosis of the bones is to be **avoided**. The abscess should not be opened, as it will usually absorb, even when very large. Should the pain be excessive or the constitutional symptoms grow



FIG. 16.—RACHITIC DEFORMITY. Anterior bowing of the tibiae.

markedly worse, it may be necessary to **open** a tuberculous **abscess**. In these instances, the abscess cavity should be opened by large incisions and thoroughly wiped out with gauze. Drains are placed and the incisions gaped as wide as possible. In the after-treatment no injections or irrigations should be used. Where a careful Carrel-Dakin technic has been carried out in tuberculosis of the bone, the results have not been as satisfactory as in ordinary bone-abscess.

PROGNOSIS.—In the majority of cases treated early the outlook is

favorable. Much depends upon the surroundings of the patient, upon the general condition of the patient, and upon the power of resistance against the tubercle bacilli. If these conditions are satisfactory the prognosis is very favorable.

PATHOLOGY.—Tuberculosis of the bones and joints usually begins in the spongy tissue of the epiphysis, or in the juxta-epiphyseal and adjacent region. After the stage of tuberculosis infiltration the process



FIG. 17.—BOW-LEGS DUE TO RACHITIS.

takes one of three forms—namely, the infiltration absorbs, **breaks** through the periosteum and discharges, or produces an **arthritis**. “Cold” abscess may be formed about the joint. The contents **of** the abscess may be quite thick or else watery. Tubercle bacilli may be **found**, but pyogenic organisms are absent. Repair takes place by the **formation** of fibrous tissue. Cartilage or bone may be laid down in the **process** of repair. An *x-ray* examination, when the disease has **progressed** sufficiently, will show a small focus in the bone, marked atrophy **in** the bone, and a decrease in the size of the cortex as compared with **that** on the unaffected side.

Tuberculosis of the Spine (Pott's Disease).—This condition is characterized by more or less destruction of the bodies of the vertebræ, the process being slow (Fig. 23). As the bodies are progressively destroyed a marked kyphosis is formed (Figs. 24 and 25). With the increase of the kyphosis, pressure symptoms on the cord may be noted, even to the point of destruction.



FIG. 18.—RACHITIC DEFORMITIES. X-ray.

ETIOLOGY.—Tuberculosis of the spine is a disease which attacks male and female alike. Any of the vertebræ may be involved. A generally lowered resistance is the predisposing cause, while a jar or blow may be the localizing cause.

SYMPTOMATOLOGY.—In the untreated cases there is often a marked decline in the general condition of the patient, with loss of flesh. Very often, however, this is not noticed early in the disease. The patient carries the spine carefully, stoops cautiously in picking up articles

from the floor, and in sitting will often use his hands to steady the spine by leaning as he sits, lifting the weight of the shoulders or the weight of the head with his hands. Very often the patient will complain



FIG. 19.—KNOCK-KNEE DUE TO RACHITIS.

of abdominal or chest pain, due to congestion or pressure on the nerves coming from the spinal canal. Sleep is often disturbed suddenly at night by bad dreams or, in children, by night cries. The patellar or other reflexes are usually increased. There is a marked muscle-spasm in the region of the disease. With tuberculosis in the cervical region

there may be a slight torticollis accompanying the spasm of the cervical muscles (Fig. 26). In the dorsal region the spine is held rigidly by the muscles. In the lumbar region there is more or less psoas contracture, depending upon the severity of the condition, with a limitation of the hyperextension of the leg. As the disease progresses a large or small knuckle is formed, depending upon the number of vertebræ involved, and the amount of destruction of the bodies on the vertebræ.



FIG. 20.—ACHONDROPLASIA.

As the spine bends backwards there is more or less compression of the cord, increasing the reflexes, especially the knee-jerks, and the psoas spasm, and, when extreme, causing ankle-clonus. Abscesses occur in tuberculosis of the spine, as in tuberculosis of the joints. Abscess in cervical Pott's disease may appear as a deep cervical abscess or as a retropharyngeal abscess. In the dorsal region it may appear on one side of the spine or may extend into the mediastinum, causing pain, cough and dyspnea, or it may rupture into the lung. In the lumbar region it appears as a psoas abscess. If

the disease has progressed sufficiently the *x*-ray examination will show a focus in the body or an anteroposterior flattening of the body. The intervertebral disk may be obliterated or destroyed and the process may be shown to involve several vertebræ.

DIFFERENTIAL DIAGNOSIS.—In the cervical region, tuberculosis of the spine may be differentiated from *congenital torticollis* by the following characteristics of the latter ailment: facial asymmetry, the un-



FIG. 21.—ACHONDROPLASIA, SHOWING FLATTENING OF THE VERTEBRÆ.

even pull of the muscles, the freedom from pain, the lack of general constitutional symptoms, the absence of neuralgic pain, the absence of characteristic attitude and the support of the head with the hands, and the absence of thickening of the tissues at the site of the disease. The presence of an abscess will often settle the diagnosis as far as *torticollis* is concerned. It must not be forgotten, however, that irritations of the scalp, or disease of the tissue or tonsils often cause enlargement and irritation of the cervical lymph-glands, simulating disease of the spine. Ear conditions may be differentiated by the local examination, the tenderness about the mastoid being diagnostic.

In *meningitis* the disease generally begins abruptly with a chill. Vomiting, headache, excruciating pain, and Kernig's sign are almost always present; delirium is rarely absent; there is extreme cutaneous hyperesthesia and nystagmus, a temperature of from 101° to 103° F. (38.33° to 39.44° C.), and usually leukocytosis. Tuberculous meningitis sometimes follows tuberculosis of the bones in the spine and elsewhere; its onset is usually very gradual. *Traumatic conditions* of the spine, with symptoms developing long after the injury, are sometimes difficult to differentiate from tuberculosis of the vertebræ, but the re-



FIG. 22.—ACHONDROPLASIA. X-ray of the knee.

covery under treatment will not take as long as in Pott's disease. In certain cases it is necessary to give protective treatment before a certain diagnosis can be made.

In *rheumatism* the onset is usually sudden, and under proper treatment the symptoms will subside. The kyphos may be very marked in the dorsal and lumbar spine in tuberculosis.

TREATMENT.—*General Treatment.*—The early treatment should be **recumbency** in a posterior **plaster shell, hyperextended** at the point of the knuckle. This separates the bodies of the vertebræ at the points of disease and allows the proper rest and repair. The hyperextension is gradually increased. The treatment need not be painful. When the local symptoms have subsided, if the reflexes are not exaggerated a

well-fitting brace or plaster of Paris jacket should be used until the disease is completely cured. In cases in which the deformity is marked recumbent treatment should be introduced to correct the deformity. The Pittsburg frame which hyperextends the knuckle freely or the gradual increase of hyperextension in the plaster shell will almost entirely overcome the deformity in most cases. Where paralysis is beginning or has existed for any length of time, the recumbent posi-

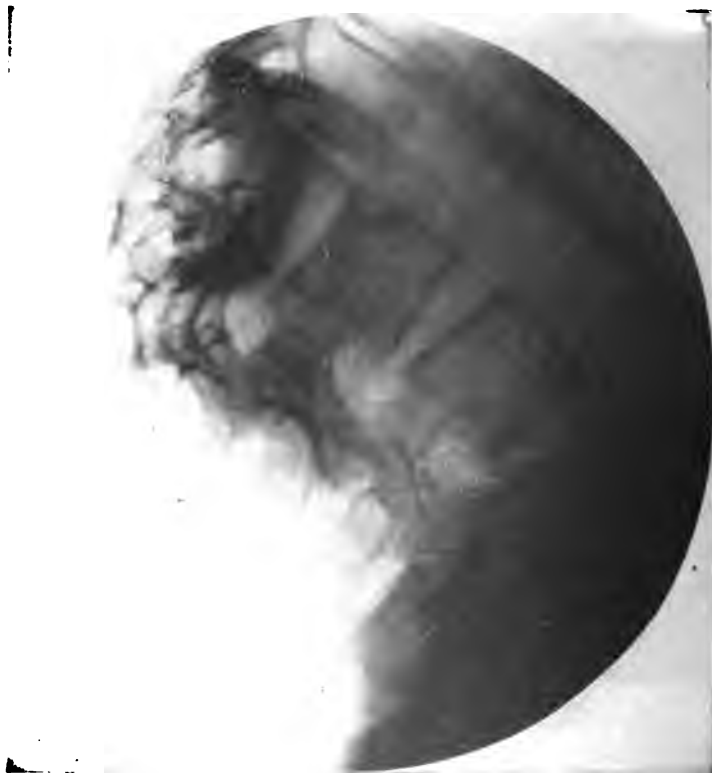


FIG. 23.—TUBERCULOSIS OF THE SPINE. Note the destruction of the bodies of the vertebræ.

tion on a hyperextended posterior plaster is the best treatment. The extent of the kyphosis, and any change in it, should be measured. This can be done by fitting a strip of sheet lead to the contour of the kyphos and then making a tracing on cardboard. The accuracy of the tracing should be tested by fitting the cardboard to the kyphos. Once this is obtained, any change in the kyphos can be readily detected.

Plastic Operations for Fixation of the Spine.—Operations for fixation of the spine in the region of the disease have been used with a good

deal of success. At the Children's Hospital in Boston and in general orthopedic practice, the operation is not done on children, as a rule, unless the deformity is increasing, or where the best possible care is not available at home. There are some exceptions to this rule.

In adults, however, the operation is distinctly advisable if performed by experienced clinicians, as it usually shortens the convalescence by from three to five years. The spine should be immobilized



FIG. 24.—TUBERCULOSIS OF THE SPINE WITH SMALL KYPHOS.



FIG. 25.—TUBERCULOSIS OF THE SPINE. Neglected case, large kyphos.

above and below as well as in the region of the kyphos. Careful technic is very important. Dr. Hibb's operation is performed by **bending down the spinous process** in one line, forming with the periosteum a bony ankylosis in the region of the kyphos. Dr. Albee's operation consists in removing a long **graft** from the tibia and placing it between the split spinous processes. When performed by a surgeon thoroughly familiar with the technic, these operations are extremely valuable. It must be remembered, however, that these operations fix the spine, but

by fixing the spine help to cure the disease. The patient must still take care of his general health and of his spine until he is entirely well. In recovering from Pott's disease the **general health** and activity should be **carefully guarded**. The improvement of the general health and local symptoms goes hand in hand with the local cure. Tuberculosis of the spine is distinctly amenable to treatment. Disease at any one level should be treated by fixation by apparatus holding the pelvis, dorsal and lumbar spine. Where the disease is above the sixth dorsal vertebræ, the cervical spine should be held.



FIG. 26.—TUBERCULOSIS OF THE SPINE. Note the marked kyphosis.

PATHOLOGY.—See Tuberculosis of the Bones and Joints.

Periostitis.—Periostitis is an infectious condition of the periosteum. In syphilitic periostitis the periosteum may be stripped and elevated, the whole process being painless. A periostitis due to pyogenic bacteria rarely occurs without some infection of the bone below, and for that reason it may be considered with that condition.

Osteomyelitis.—**ETIOLOGY.**—Osteomyelitis is usually produced by the pyogenic bacteria. Occasionally the pneumococcus or the typhoid bacillus may cause the process. The femur, the tibia and the humerus are the bones most commonly affected (Fig. 27).

SYMPTOMATOLOGY.—The symptoms may be mild and the pain slight or very severe, with sudden onset, high temperature extending to 106° F. (41.11° C.), great pain, swelling, tenderness, local heat, redness or



FIG. 27.—OSTEOMYELITIS OF THE FEMUR.

surface edema, the appearance of grave illness, delirium resembling a typhoid condition and a greatly increased white-cell count. The virulence varies, the process is destructive, the bone is destroyed, sequestræ form, and the pus extends up and down the bony canal and strips the periosteum from the bone. If the disease is near or involves the epiphysis, the growth of the bone will be seriously impaired.

DIFFERENTIAL DIAGNOSIS.—*Syphilitic gumma* with destruction of the bone or of the joint often resembles osteomyelitis, although the pain is not as severe. In syphilis the process is more extensive than the discomfort or pain would suggest. The *x-ray* will show syphilitic characteristics. In doubtful cases the blood examination will aid in making a diagnosis.

Tuberculosis of the bone is in the epiphysis, while osteomyelitis is in the shaft. In some chronic osteomyelitis cases it is hard to differentiate between the two conditions.



FIG. 28.—POLIOMYELITIS. Paralysis of the deltoid.

TREATMENT.—An osteomyelitis or periostitis, when not syphilitic, should be **operated** upon as soon as possible. The severe cases with delirium should be operated upon immediately, the mild cases within a few days. Judgment must be used, however, with each individual mild case and the time of operation will depend upon circumstances.

An **incision** should be made on both sides of the bone with draining down the bone and small openings into it. When it is possible, an *x-ray* examination should be made before operation, so that the exact locality of the disease may be determined.

PATHOLOGY.—The bone-marrow is primarily affected. The process may be spread extensively in the marrow before it pierces the cortex. Suppuration is produced between the bone and the periosteum. Later an abscess is produced in the soft parts. This may evacuate, draining through a sinus. It is an infection of the bony cortex. It may be limited to this cortex or involve the periosteum, or the cortex, and extend to the bony canal.

Typhoid Spine.—In this condition there is pain, disability and stiffness in the spine following typhoid fever. The temperature is slightly elevated but irregularly so.



FIG. 29.—DEFORMITY OF THE SPINE DUE TO POLIOMYELITIS. Note the extreme paralysis of the back and leg muscles.

TREATMENT.—The treatment consists in general **hygiene, rest, heat, gentle massage** and later a light **support and exercises** to strengthen the back muscles.

Infantile Paralysis.—**ETIOLOGY.**—Infantile paralysis is an infectious disease. It may occur at any age, but usually it appears in childhood.

SYMPTOMATOLOGY.—At the **onset** there is usually fever, pain, and tenderness at the back and extremities, vomiting and convulsions. The paralysis comes on shortly after the other symptoms and quickly reaches its maximum. It then usually remains stationary for a variable period, lasting from a few days to several weeks. Sometimes the paralysis is noted without any other symptoms (Fig. 28). If the condition is not treated, a permanent stationary period is reached, during which the deformities and contractures occur. The paralysis is usually motor and is of the flaccid type. The paralyzed limb may be cold and bluish, and atrophy begins soon after the paralysis and may be quite marked. The reflexes are lost, depending upon which nerves are involved (Fig. 29).

After a few months, when all improvement in the paralysis has ceased, the deformities begin to appear. These may be due alone to atrophy of the muscles or to position, to superincumbent weight, to the contraction of uninjured muscles, whose opposing groups have been paralyzed, or to unequal growth. The deformities occur most often in the legs and spine (Figs. 30 and 31). If paralysis is complete, a flail-like deformity of the leg results. This is not usually the case.



FIG. 30.—INFANTILE PARALYSIS WITH EQUINOVARUS DEFORMITY.

There may be flexion of the thigh, with knee-flexion. If all the muscles are lax there is hyperextension and lateral motion in the knee, and the weight is often borne on the ligaments. The tibia may be dislocated anteriorly or subluxated.

Talipes equinus or equinovarus, talipes calcaneus and calcaneovalgus are the common deformities of the feet. Later curvature of the spine may result from the tilting of the pelvis due to paralysis of one leg, or to faulty position due to paralysis in some other locality, or to unilateral paralysis of the muscles of the back or abdomen.

Dislocation of the hip may be present, due to either complete laxity of all of the muscles, or to unequal tension of the muscles.

The very mild cases may be extensively paralyzed at first, and then recover completely, or completely except for a few muscles.

TREATMENT.—General Treatment.—During the acute stage care should be directed to the general condition. The patient should be given as much **food** as he can assimilate, in small and frequent quantities, to prevent lowering the vitality. The **limbs** should be **wrapped in cotton** and the pressure of the bed-clothes prevented by **cradles**. Small quantities of **alcohol** should be given **internally**. During the paralytic



FIG. 31.—BRADFORD FRAME AND LONG CALIPERS APPLIED TO THE LEG.

stage the treatment should be directed toward the prevention of deformity and the regaining of muscle-power. The general procedure in preventing deformity is to gently **stretch** and **move the extremities** in the normal arc of joint-motion, by means of suitable apparatus. **Muscle-training, massage, baking, etc.**, will help to restore muscle-power.

VOL. VI.—31.

Mechanical and Operative Treatment.—A great deal can be done by mechanical means to correct deformity, maintain correction and to aid in locomotion. Operative measures are available for the relief of contracture, for stabilizing joints, for correction of deformity and for redistribution of the unparalyzed forces by means of tendon and muscle transference.

Slight cases can be benefited to a very considerable degree. Even cases with complete leg, back and abdominal paralysis can usually be helped. In many of these extreme cases, if the hands and arms are spared, locomotion is possible by means of apparatus.

Very much can be done to improve the condition of the patient who has been crippled in consequence of poliomyelitis. So much is available that it is a question requiring only study of the case, experience and some judgment to make a choice of procedures.

PROGNOSIS.—The prognosis as to life is good in the spinal type. In the ascending type with medullary involvement, the prognosis is poor, death resulting usually from respiratory paralysis. The prognosis as to deformity is more favorable under treatment and where the paralysis is not too extensive.

PATHOLOGY.—The disease is a hemorrhagic myelitis, usually involving the cells of the anterior horn. Atrophy of the muscles follows the degeneration of the cells. The extent of the muscular atrophy depends upon the extent of the spinal injury. The process is usually limited to the spinal cord but may involve the medulla and the brain. The muscles, skin, bone and all of the tissues may atrophy, depending upon the amount of cord involvement.

NON-INFECTIOUS PARALYSES

Cerebral Spastic Paralysis.—In cerebral spastic paralysis there is a loss of brain substance from hemorrhage, thrombosis, embolism, or following an acute infectious disease such as certain cases of syphilis and cerebrospinal meningitis. The reflexes are increased, and there is a tonic contracture of the affected muscles, aggravated by intentional effort. The condition may be hemiplegic, diplegic, paraplegic or monoplegic.

The intelligence is sometimes affected, either slightly or extremely. The child may be only backward, or idiotic. Sometimes epilepsy is present from the start, or it may develop as the child grows older. Often it will disappear in adult life. If the case is not treated there is more or less paralysis of motion, and slight or extreme contractures and deformities, due to the tension of the affected muscles (Fig. 32). The disability will depend upon the rigidity, the coördination and the deformity. The most common contractures are flexion of the hip, knee-flexion, subluxations of the knees, equinus, inward rotation of the shoulder, pronation of the forearm and flexion of the wrist.

Almost all of the deformities are possible, but the above are the more

common. In extreme cases patients cannot coördinate enough to use their arms or legs voluntarily—they cannot sit up or move. Fortunately these patients are usually idiotic, and so do not realize their condition.

TREATMENT.—In mild cases, they may be enabled by **muscle training** and the proper and **intermittent use of braces**, to coördinate so well that the condition cannot be noticed. Patients who cannot walk because of contractures may be relieved by **operation**, after which braces



FIG. 32.—SPASTIC EQUINUS.

may be used which will help in locomotion. By training in coördination the braces are gradually rendered unnecessary. Almost all cases may be improved. The slight cases are greatly improved. **Tenotomies, myotomies, fasciotomies, tendon-transplantation, silk ligament and tendon-fixation** are all operative measures of value in special cases.

Spastic Spinal Paralysis.—Spastic spinal paralysis is due to a degeneration or lesion in the pyramidal tracts. The condition is similar to the spastic condition due to cerebral spastic paralysis, but there is no cerebral involvement and the prognosis is more favorable.

Obstetrical Paralysis.—Obstetrical paralysis is due to the stretching, tearing or crushing of the brachial plexus at birth. There is hemorrhage or rupture in the nerve-sheath between the clavicle and the first rib. There are three types: the upper arm type, involving the fifth and sixth cervical nerves; the lower arm type, which is very rare; and the complete arm paralysis. In the upper arm type the injury is in the nerve-plexus, or above it close to the intervertebral forearm. The shoulder-muscles and those of the upper arm are weak or paralyzed. The arm is short. The forearm escapes, although it may be weak. In this type there may be adhesions or luxations about the shoulder. If the forearm muscles are weak, they may be trained and developed. The deltoid, infraspinatus serratus, teres major and minor, biceps, brachialis anticus, supinator longus and brevis, and coracobrachialis are affected, varying with the nature and extent of the condition.

TREATMENT.—The treatment consists in **muscle training, exercise, with support** to prevent overstretching of the weak muscles, **manipulation, stretching of the shortened muscles**, and in cases with contractures, of **muscle lengthening or myotomies** as the case requires. Myotomy of the subscapularis (the Sever operation) is indicated.

In the forearm and arm types, **exercises, manipulation and massage** are sometimes beneficial. In the new-born the pectorals and inward rotators and adductors of the shoulder should be gently **stretched** several times a day, also the flexors of the elbow, wrist and fingers and the pronators of the forearm. This will allow the unaffected muscles a chance to grow, and will also prevent severe contractures which might render function difficult.

OTHER PATHOLOGICAL CONDITIONS OF THE BONES

Progressive Muscular Atrophy.—There are several types of progressive muscular dystrophy or atrophy which deserve separate mention.

HAND AND FOREARM TYPE (*Aran-Duchenne*).—This form occurs in adults over twenty-five years of age and very rarely in children. The anterior horn of the cord is involved. There is a little pain, and loss of power and atrophy of the hand, especially of the thenar and hypothenar muscles of the hand. The interossei lumbricales, the flexors and extensors of the forearm, atrophy. In the later stages there is a condition of muscular contracture, and a characteristic claw-hand deformity. The body and lower extremities atrophy and sensation is unimpaired.

PERONEAL TYPE.—The peroneal type is hereditary, and occurs early and practically always under the age of twenty years. There is no cord lesion. It is a peripheral motor-nerve degeneration, affecting the nerves controlling the muscles of the hands and feet. As atrophy progresses there may be deformity and slight hyperesthesia. Sensation is rarely impaired.

ANGEL-WING TYPE.—Juvenile atrophy (Erb) occurs in later childhood and involves the serratus magnus, the pectoralis, trapezius, rhomboidei and latissimus dorsi. These muscles weaken and later atrophy, causing the characteristic “angel-wing” deformity. The back, thigh, and later the lower leg muscles gradually weaken. The disease process is very slow and does not progress sufficiently to give a total paralysis. The condition is incurable.

LARGE CALF TYPE.—Pseudomuscular hypertrophy occurs between the ages of five and ten. There is a marked muscular weakness in the thigh and back, with atrophy and weakness in the leg, and enlargement of the calf due to the presence of fat and fibrous tissue, giving the appearance of strength here. The arms are only slightly affected. There is a shuffling gait and great difficulty in rising from a prone position. Sensation is not affected. There is no recovery and very few live beyond young adult life.

FACE AND SHOULDER TYPE (*Landouzy-Déjerine*).—The face muscles are atrophied, giving a dull, flaccid appearance. The muscles of mastication and of the eye are never affected. The atrophy spreads to involve the shoulder and arm muscles.

These types may be divided into the: (a) myopathic, including all but the Aran-Duchenne cases, and (b) myelopathic, consisting of the Aran-Duchenne cases. The latter are classed as myelopathic.

Infantile Scurvy.—This condition may be slight or severe. In mild cases there is debility, and poor physical condition. As in orthopedic conditions, the patient is usually brought for treatment suffering from pain or fracture in the long bones. With this pain, which may be extreme, there is anemia, spongy gums, purpuric spots, and swelling along the painful areas. X-rays show subperiosteal hemorrhages and often more or less complete fractures. The spine is rounded outward and backward, and in extreme cases the infant has thin, senile features.

TREATMENT.—The child should be kept quiet on his back on a **Bradford frame** so that he may be moved without jarring the tender extremities. A curved frame may be used. The patient should be given **small and frequent feedings** adapted to his age, with **orange juice** twice daily. The improvement is usually very marked in six or eight weeks.

Congenital Torticollis.—Congenital torticollis is an asymmetrical carriage of the head on the shoulders due to the asymmetrical development of the vertebræ or ribs or to asymmetrical pull or development of the muscles. There is usually a facial asymmetry due to the unilateral pull. This in time becomes less pronounced. There is rarely any pain. The movement of the head is very much or only slightly restricted to one side. When it is the muscles which are affected, the sternomastoid is more frequently found to be contracted than any other muscle. The posterior muscles may be contracted with or without the anterior.

TREATMENT.—**Stretching, massage, and exercises** are of little and only very temporary value. The treatment of choice is **section of the contracted muscle**, including its anterior and posterior sheaths. No

fibers should be left uncut. This may be done through a very small incision, as the skin just above the clavicle may be stretched outwardly or inwardly and the entire sternomastoid muscle easily reached. The important element of cure is to hold the head in an overcorrected position by **apparatus** for from ten to twelve months after operation (Fig. 33). The results are uniformly successful. When the condition is due to bony malformation or to asymmetry which cannot be corrected by exercises, further asymmetrical development may be prevented and the growth guided in the right direction by a **brace**. Neglected cases



FIG. 33.—TORTICOLLIS, SHOWING POSTOPERATIVE BRACE.

of congenital torticollis produce chest and spinal deformities in time. It is therefore important to treat the cases as early as is practical. Operation is rarely advisable until the patient is about five years of age.

Acquired Torticollis.—Acquired torticollis generally begins in childhood, except the spasmodic form which occurs in adults.

ETIOLOGY.—Acquired torticollis may be due to acute infection of the glands or of other tissues of the neck. It may be attributable to

direct limitation of the muscles or to reflex irritation of the nerves, occurring in nasopharyngeal or ear diseases, or in arthritis. The spasmodic type is of unknown etiology. Torticollis sometimes results from deep scars due to bursitis or to other trauma. Unequal vision, and faulty attitude in working, may be causes. Typesetters are of this class.

TREATMENT.—The treatment is at first to combat any obvious cause. If the torticollis is well established, **rest, exercises, braces and jackets** will aid in the correction of the deformity.

In spasmodic torticollis the treatment is by fixation. **Resection of the spinal accessory nerve** has been recommended, also **myotomy** of most of the neck-muscles. This should be resorted to very rarely, if at all. Resection of the sternomastoid muscle is not sufficient, as in acquired torticollis too many other muscles are involved.

Sciatic Scoliosis.—There may be changes in the contour of the spine due to chronic sciatica. The patient will bend away from the painful part, adducting the affected limb to relieve the tension on the nerves. There results, if this condition is chronic, a lateral lumbar curvature with the convexity opposite the affected limb. At the same time there is a loss of the normal lumbar lordosis. Later there may be a compensating curvature higher up in the spine.

TREATMENT.—It is necessary first to **find the cause of the sciatic pain and to relieve it.**

If the condition is due to strain it should be treated in the same way as sacro-iliac injury and other lame back conditions. As the back improves the sciatica will improve as well. The possibility of arthritis, proliferative, toxic or infectious, must not be forgotten.

Back-strain.—Back-strain is a condition often described by various authors under the names of irritable spine, hysterical spine, weakness of the spine, etc.

ETIOLOGY.—The condition is most common in adolescent and young adult women, and is rarely found in children. It usually affects patients who are under par physically, or who are of an emotional and excitable temperament or have been subject to business strain or social high tension. Most authors describe the affection as being the result of trauma, or of overuse or overstrain of the back-muscles.

SYMPTOMATOLOGY.—Pain is prominent as a symptom. There is also irritability and sensitiveness in the spine. All symptoms are aggravated by voluntary motion. There is often muscular rigidity. This may be unilateral.

TREATMENT.—Treatment should be directed toward the cause of the affection. The back-muscles should be rested by **recumbency**. When it is necessary the patient should recline for a part or all of the time at first. Later the back may be supported by a **brace corset** or by **adhesive strapping** temporarily and by recumbency part of the time. The real means of cure consists in **exercises** which cultivate a correct standing position.

Osteogenesis Imperfecta—Fragilitas Ossium.—Infants with osteogenesis imperfecta rarely live over a year. Occasionally they live beyond childhood, but only rarely. The bones are very brittle, multiple fractures occur in a short time; often they are painless. All of the bones are equally susceptible. The callus formation is small; the medullary cavity is increased at the expense of the cortex. The bones of the skull ossify imperfectly. In the long bones, the trabeculae show imperfect bony lamination; the corpuscles are oval, not stellate. There are no canaliculi between the lacunae.



FIG. 34.—OSTEOMALACIA, SHOWING SPONTANEOUS FRACTURE OF THE FEMUR.

Osteomalacia.—Osteomalacia occurs chiefly in adult life, although sometimes in childhood. The bones bend and break easily (Fig. 34). The condition is one of faulty nutrition, with a decrease in lime salts and phosphorus in the bone, a richness in magnesium, and an increase in sulphur. The shaft and ends of the bones are affected alike. The bones are thinned and softened.

TREATMENT.—The treatment is unsatisfactory. It consists of general hygienic exercises and care in the diet.

Osteitis Deformans (Paget's Disease).—In Paget's disease the bones soften, enlarge and curve. It occurs in later life from forty years of age on. It is usually accompanied by a certain degree of arteriosclerosis. There may be intense pain in the curving long bone. The tibia is more apt to be affected; it becomes rounded and saber-shaped (Fig. 35). The patient walks stiffly and awkwardly as the condition progresses. The



FIG. 35.—PAGET'S DISEASE.

back becomes round, the head enlarges, and the bowing of the whole leg increases.

TREATMENT.—General hygiene and local heat and flannel protection help to decrease the pain.

Painful Heel—Bursitis (Policeman's Heel).—There is pain and sensitiveness at the bottom of the heel. This may be due to undue pressure at that point, or to an inflammation of the bursa under the os calcia,

or to sudden or prolonged strain at the attachment of the plantar fascia. This condition should not be confused with disease of the bone or periosteum. An *x-ray* examination will aid in diagnosis.

TREATMENT.—The treatment consists in removing the pressure or in modifying it by pads; in extreme cases, immobilization, and, when the patient is walking, poultices and counterirritants will be necessary.

Ingrown Toe-nail.—**TREATMENT.**—Operation under local or full anesthesia is indicated. A tourniquet may be applied at the base of the toe. The overlapping tissue is removed by two parallel longitudinal

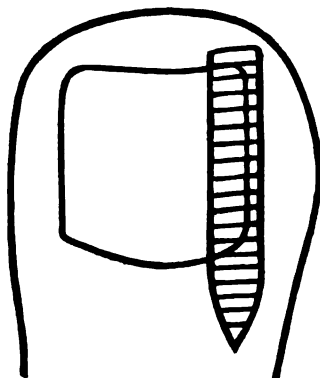


FIG. 36.—TISSUE AND PART OF NAIL REMOVED FOR INGROWN TOE-NAIL.

incisions. One incision splits the nail a full quarter of an inch from its lateral edge and is continued through the matrix to the bone. The other, running parallel to the first, is made through the skin beyond the nail, and is carried down to the bone. These parallel incisions are continued through the base of the nail for nearly half an inch, but should not reach the joint. The nail and tissue between these incisions are removed (Fig. 36). The gap is closed by sutures passed through the remaining nail and the edge of the skin.

Hallux Rigidus.—This condition is characterized by pain and limitation of motion in the great toe. It may be due to the constant pressure of an ill-fitting shoe, to trauma, contracted capsule or to old arthritis.

TREATMENT.—The treatment includes the wearing of properly fitting shoes, of local heat and applications, with protection from all pressure and motion until the symptoms have disappeared.

Hallux Valgus (*Abduction of the Great Toe*).—**TREATMENT.**—When slight, this may be corrected by exercises, by stretching the ligaments,

by wearing **straight-lined shoes**. When the condition is extreme, an **operation** may be necessary. The head of the metatarsal, so necessary in weight-bearing, should not be removed. **Osteotomy** may be performed, or a **wedge removed** at the neck of the bone. These operations are often contra-indicated in rheumatic patients (Fig. 37).

Hemophilic Joint Swelling.—This condition usually occurs in so-called “bleeders.” The hemorrhages often occur with very slight



FIG. 37.—HALLUX VALGUS.

trauma. The hemorrhage is in the tissues about the joint as well as in the joint itself.

TREATMENT.—**Rest** and sometimes **fixation of the joint** are indicated immediately after trauma and during the acute swelling. If the swelling is very slight this will not be necessary. The use of **horse serum** injected subcutaneously, not near the joint, and the judicious use of **exercises** to tone up the general condition, are indicated.

DISEASES OF THE JOINTS**DISLOCATIONS**

Congenital Dislocation of the Hip.—**ETIOLOGY.**—In congenital dislocation of the hip, the hip may be very slightly dislocated, in which case the head of the femur slides insecurely in the acetabulum and just over its rim; or it may be markedly dislocated, the trochanter being near the crest of the ilium.



FIG. 38.—CONGENITAL DISLOCATION OF THE HIP.

SYMPTOMATOLOGY.—There may be little or a great deal of disability at first. Usually when the child begins to walk there is a noticeable limp which gradually increases. Later there may be a very marked rolling gait. The limp is more noticeable when the condition is single than when a double dislocation exists. The trochanter will be found above Nelaton's line (a line connecting the anterior superior spine of the ilium and the tuberosity of the ischium). The mobility of the trochanter up or down as the patient walks or as the leg is pulled, or

when the patient is lying down, will be noticed. The perineum is broader. There will also be a Trendelenburg sign. (This sign is obtained by making the patient stand on one leg and raise the opposite knee. The physician faces the back of the patient and watches the line of the buttock. If the hip of the leg on which the patient stands is dislocated, the opposite buttock drops.) There is a very marked shortening of the affected leg (Fig. 38). With a dislocated hip, there



FIG. 39.—CONGENITAL DISLOCATION OF THE HIP, SHOWING POSTOPERATIVE PLASTER AND POSITION IN BED ON A BRADFORD FRAME.

is more motion. Motion in inward rotation and adduction may be extreme. The length of the capsule allows very great freedom of motion in the young child. As the patient grows older the capsule becomes shorter and there is more limitation and sometimes very little motion. The capsule is thickened and often constricted, due to the pull and due to the lack of lateral stretching of its fibers. The cotyloid ring is narrowed, making reduction more or less difficult. There is disability from the limp

and especially from the acquired deformities due to the shortening of the muscles and the later limitation of motion. Lordosis becomes extreme. There is pain in the back and often pain in the hip due to the lordosis, to the hip flexion and limitation of motion. The patient walks on the toe of the shortened leg.

An x-ray examination of a congenital dislocation of the hip will often show a shallow acetabulum when the acetabulum is really not shallow. This is due to the increased radiability of the cartilaginous edge. The head of the femur is often smaller, and there is more torsion in the neck than in normal cases.

DIFFERENTIAL DIAGNOSIS.—Congenital dislocation of the hip is not easily confused with other conditions, except perhaps dislocation due to acute arthritis of infancy. In this type of case the head of the bone is likely to be partly or totally destroyed and there is apt to be a small scar on the skin from one-quarter to one-half an inch in diameter where the abscess discharged itself in infancy. An x-ray examination will of course be an aid in diagnosis.

TREATMENT.—The treatment of a congenital dislocation of the hip consists in reducing the dislocation by **manipulation** under ether and in **maintaining the reduction** long enough to allow the ligaments to actually shorten and the bones to grow, so that the capsule and ligaments will tighten. The corrected position should be maintained by appliances for from ten to twelve months (Fig. 39). The best position for after-treatment is one with the leg abducted 90 degrees and flexed 90 degrees. In a case which has been well reduced, the head must be in the acetabulum and the line of the femur should be such that the knee is posterior to and above a line drawn through the anterior superior iliac spines. The best age for operative reduction is between two and one-half and seven years. By means of Dr. Bradford's congenital hip **machine**, used at the Children's Hospital in Boston and in many other cities in this country and abroad, it is possible to reduce dislocation in cases of individuals over fifteen years of age. One case was reduced at the age of twenty-four. It is inadvisable to wait longer than seven years. The patient grows older and the muscles grow strong, making the reduction proportionately more difficult.

Should the reduction by the Bradford machine fail, it is necessary, in a few cases, to make an **incision**. Operation by incision alone will not allow the head to be reduced in a congenital dislocation of the hip, unless there is some forcible means of reduction at hand to help the surgeon with the open operation. Dr. Bradford's apparatus for this purpose is most useful. Many cases may be reduced manually without a traction machine and without a congenital hip machine such as Dr. Bradford's. It is better to operate between the ages of four and eight. Cases of individuals fifteen years of age can be reduced by Dr. Bradford's apparatus. The author reduced one congenital hip at twenty-four years of age.

Whether or not the machine is used, it is important to **stretch the capsule** thoroughly before and after reducing the hip. Redisllocations

are often due to lack of proper capsular stretching. As a rule, extreme cases of torsion of the neck do not need an osteotomy. After the hip is reduced the torsion disappears in time with weight bearing. After operation, the patient is put in **plaster** which covers the pelvis, the thigh, the leg and the foot of the affected side and includes a small cuff of plaster around the unaffected thigh. It is important that the plaster should fit well and snugly cover the trochanter and the tuberosity of the ischium on the affected side, so that the plaster cannot slide up and dislocate the hip.

Snapping Knee.—This is a partial recurrent displacement of the tibia on sudden extension of the leg. The tibia is displaced forward, with outward rotation. There is often an audible snapping sound. The condition is due to weakness and laxity of the ligaments and muscles. Occasionally the sensation is produced by a slipping tendon or muscle without joint luxation. Anteroposterior relaxation following an injury is sometimes due to a torn crucial ligament.

Congenital Dislocation of the Knee.—Congenital dislocation of the knee is probably due to the position *in utero*. The ligaments of the knee are loose and the tibia is dislocated anteriorly and often laterally at the same time. When the articulation is very loose, it may be dislocated backward.

TREATMENT.—The bones should be replaced gently several times a day; with a little practice this can be done easily. If this treatment is long continued, in some cases the bones will remain in place of themselves, while in others they will have to be put in place daily in this way until the child is a year old or older. The knee is then **reduced** and held flexed by a **plaster of Paris bandage** for from six to ten months, the bandage being renewed as often as is necessary. The child is allowed to move about with the plaster on.

Congenital Hyperextension of the Knee.—Congenital hyperextension of the knee may occur with other congenital deformities such as congenital club foot, and congenital dislocation of the hip (Fig. 40). The knee is bowed backward and cannot be flexed; in some cases it cannot be straightened.

TREATMENT.—**Gradually stretching the knee** in flexion will in time overcome the mild cases. In other cases an ether **manipulation** is necessary and the knee is put in **plaster of Paris** in a flexed position, for from four to eight months. After that it is flexed regularly each day. The use of plaster of Paris should be avoided until the child is over a year old.

Congenital Dislocation of the Patella.—Congenital dislocation of the patella is often due to a lack of growth of the external condyle of the femur or to a lateral subluxation of the knee with dislocation, usually accompanied by more or less knock-knee.

TREATMENT.—When discovered early, these cases yield to the **manipulation** described under Congenital Dislocation of the Knee. If, however, the affection is not discovered until the child is six or seven years

old, it is very often necessary to correct the knock-knee by **osteotomy** and to reef the patellar ligament as described under Traumatic Dislocation of the Patella.

Traumatic Dislocation of the Patella.—A traumatic dislocation of the patella is usually outward. The patella may remain dislocated for a short time, but as a rule it slips back as the knee straightens.

TREATMENT.—Occasionally the dislocation cannot be reduced without **ether relaxation**, but after this treatment the patella readily slips into place. After a traumatic dislocation of the patella, the knee should be kept entirely straight for at least five weeks in a **plaster of Paris**



FIG. 40.—CONGENITAL HYPEREXTENSION OF THE KNEE, AND CONGENITAL CONTRACTURE OF THE HIP.

splint. This will prevent flexion and allow the torn ligaments to shorten up and heal. In recurrent dislocation of the patella, it is necessary, as a rule, to **split the patellar tendon**, cut away the lower attachment of the outer half, quilt it with silk and attach it to the inner side of the tibia. This attachment, and reefing the capsule on the inner side, will prevent future dislocation, provided the after-treatment is carefully guided for five or six weeks, to prevent much flexion of the knee.

Sacro-iliac Injury.—The sacro-iliac articulation may be injured by falls on the buttocks or pelvis, or by strains.

SYMPTOMATOLOGY.—The symptoms are pain, limping and weakness. The pain is referred to the side of the pelvis and may radiate along the buttock and thigh. There is pain on forward bending of the body, on flexion of the thigh, or on any sudden motion or jar. There may be tenderness over the articulation.

TREATMENT.—Treatment is by **support**, either with **fixed plaster bandages, adhesive straps**, or by **rest in bed**. After this, **mild exercises and proper posture** are indicated.

Bad strains will often require from six to eight weeks to overcome the severe symptoms. Following this the back must be straightened and the general health improved. The possibility of infectious, toxic, or proliferative arthritis must not be forgotten.

Subluxation of the Clavicle.—The sternal end of the clavicle may be partially displaced. This is usually due to injury. The capsule is **lax**, allowing displacement during certain motions of the arm. The reduction is easy. There may be pain and discomfort as well as weakness and insecurity.

TREATMENT.—When not severe, the displacement may be cured by **appliances** holding the clavicle in place. The joint may be opened and a small **inlay graft** taken from the clavicle and placed bridging the sternoclavicular joint.

Congenital Dislocation of the Shoulder.—This condition is rare. Dislocation may also be due to trauma at birth. The head of the bone is usually displaced backward over the scapula with abduction and inward rotation of the arm. Dislocation following obstetrical paralysis may simulate the congenital form.

TREATMENT.—Treatment is by **reduction and fixation in plaster**, with the arm abducted and outwardly rotated.

Chronic Recurrent Dislocation of the Shoulder.—Chronic dislocation of the shoulder may be due to stretching, and weakness of the capsule, to weakness and atrophy of the muscles, to paralysis or ruptured muscles and tendons. Recurrent cases are due to an unhealed slit in the capsule. The intervals may be short or long, and there is usually no inflammatory reaction.

TREATMENT.—Treatment consists in **reduction, stretching** of the capsule to prevent dislocation, and **fixation** for six weeks; later **exercises** directed toward strengthening the muscles about the joint are indicated.

Recurrent Dislocation of the Patella.—Recurrent dislocation of the patella occurs when there is a laxity of the ligaments and accidental displacement of the patella outward and toward the external condyle. It is more frequent in females than in males. There is sudden, sharp pain and disability. Later there may be an effusion in the joint.

TREATMENT.—Reduction is by **extension of the leg and pressure on the patella**, which is gently pushed into place. The knee should then be **fixed** either by **adhesive-strapping**, or in severe cases, in **plaster** for about five weeks. **Exercises** should be given to improve the muscu-

lar tone. Succeeding displacements are apt to be attended by less pain than the original one.

The operative treatment is by **splitting the patella tendon** and stitching the outer half to the periosteum of the tibia, slipping the tendon first under the inner half. Operation is advisable when there are persistent recurrent attacks.

Dislocation of the Elbow.—**TREATMENT.**—Reduction should be performed early in the condition. After six weeks the adhesions are firm



FIG. 41.—ANKYLOSIS DUE TO TUBERCULOSIS OF THE HIP.

and reduction may be impossible. **Operation and arthroplasty or excision** are indicated when a perfect reduction is not possible or when the dislocation has existed for any length of time.

TUBERCULOSIS OF THE JOINTS

Tuberculosis of the Hip.—**ETIOLOGY.**—The etiology of tuberculosis of the hip is the same as that for tuberculosis of the other bones and joints.

SYMPTOMATOLOGY.—This disease is more common in children than in adults. The focus is usually near the epiphyseal line in the neck or head of the femur. In rare cases it may be in the trochanter and sometimes in the acetabulum. The disease is sometimes so slight that there is complete recovery with perfect motion in every direction. The disease begins with a slight limp. The child may begin early to walk on the toe of the affected leg. The pain is often referred to the knee. On examination, even early in the disease, measurements will show



FIG. 42.—TUBERCULOSIS OF THE HIP.

atrophy at the thigh, at the calf, and often at the knee. Early in the disease the *x*-ray will show no bony change. As the disease progresses there is apt to be muscular spasm, noticed gradually in the upper thigh muscles on the inner side of the leg, thickening in front of or behind the trochanter, or both, distinct limitation of inward rotation, and, as the disease progresses, limitation of abduction, flexion and hyperextension of the hip. There may be marked distortion and deformity of the hip. Occasionally, the patient may irritate the condition by a twist or jar, and there is extreme pain, but during the whole course of the disease pain is comparatively absent, unless an abscess is forming. Abscess may

occur as in other joints. It may rupture spontaneously, or it may be absorbed. The abscess may burrow along the muscles and come to the surface at a joint distant from the actual site of the disease. One of the marked points of diagnosis that differentiates tuberculosis of the joint from other joint diseases is the early atrophy, which is out of proportion to the history of the disease (Fig. 41). When the disease has progressed over a long period of time there is atrophy from disuse



FIG. 43.—TUBERCULOSIS OF THE HIP. Acute condition.

in addition to the atrophy due to the disease. During the progress of the disease there may be so much thickening about the joint that there is no motion at the hip (Figs. 42 and 43). Double hip disease may occur. In a case that has been properly treated and is under treatment this does not signify permanent ankylosis. As the disease progresses to recovery the thickening disappears and the motion may entirely return in favorable cases.

TREATMENT.—The leg should be **fixed by traction and by immobilization in bed**, with the femur pointing in the direction in which it is held by the spasm of the muscles. As the spasm of the muscles de-

creases the leg may be brought down to the straight position. As the acute symptoms subside a well-fitting Bradford abduction hip splint should be applied. The patient is accustomed to these splints during the day, and the bed traction splint is applied at night. Later a high sole is applied to the shoe on the good leg and the patient is allowed to walk with a traction splint and crutches. This treatment should be kept up until there is restoration of motion and complete recovery from the disease. This may take from one to five years.



FIG. 44.—TUBERCULOSIS OF THE KNEE. Acute condition.

PROGNOSIS.—Death may occur from generalized tuberculosis or from some intercurrent disease. Both are favored by poor surroundings and by the poor general condition of the patient.

The majority of cases do well under proper surroundings and hygiene, and recover with more or less deformity. The earlier the treatment is begun, and the more attention is given to the general condition of the patient, the less is the resulting deformity, other things being equal. Complete recovery without loss of motion or deformity occasionally occurs, but is not common.

PATHOLOGY.—See the Pathology of Tuberculosis of the Bones and Joints.

Tuberculosis of the Knee and Ankle.—**ETIOLOGY.**—The etiology of tuberculosis of the knee and ankle is the same as the etiology of tuberculosis of the other bones and joints.

SYMPTOMATOLOGY.—There is usually swelling about the joint (Fig. 44). Pain is found to be comparatively absent when the whole course of the disease is considered. Occasionally, there is slight local heat



FIG. 45.—ANKYLOSIS CAUSED BY TUBERCULOSIS OF THE KNEE.

but very often there is none and the disease is characterized as a white swelling. The atrophy of the calf and thigh is very marked early in the course. When the disease is sufficiently advanced, any *x-ray* examination will show the focus and atrophy of the bone (Fig. 45).

TREATMENT.—The joint should be protected from motion and jar by a well-fitting **plaster of Paris** covering and a **Thomas knee-splint**. Traction is not necessary. At night the Thomas knee-splint is removed, but the plaster is left in place. If the joints are well protected from jar and motion the disease which is at the epiphyseal line will rarely

extend into the joint, even if an abscess is present. **Excision** is sometimes justifiable in adults, when the disease is extensive. In children this method should almost never be employed.

PROGNOSIS.—In children treated early in the disease there is usually complete recovery of motion. In adults, the progress of the disease is slower and there may be joint involvement early in the course.

PATHOLOGY.—The pathology of tuberculosis of the knee and ankle is the same as that discussed under the Pathology of Tuberculosis of the Bones.

Synovial Tuberculosis.—Synovial tuberculosis occurs primarily, or secondary to tuberculosis of the bone. If the joint is opened, a hypertrophied, diseased capsule with more or less fluid will be found.

TREATMENT.—**Incision** and removal of the focus, if local, is often indicated. When this is not effective, it may be necessary in extreme cases to **remove** the whole capsule and synovial membrane and to attempt to obtain ankylosis by erosion of the joint.

Rice Bodies.—Rice bodies are small, white, lentil-shaped or ovoid bodies sometimes found in disease of the synovial membrane of the joints, or in tenosynovitis. They are more apt to be present when the disease is tuberculous.

There is usually a peculiar crepitus about the tendon sheath in this condition, but when the bodies are present in the joint they are usually found during an operation on the joint.

SYMPTOMATOLOGY.—The symptoms are usually weakness, and inability to use the affected joint or tendons with any great force or precision. The patient complains of disability and discomfort, and later the swelling is noticed.

TREATMENT.—The tendon sheath or synovial cavity of the joint should be **incised**, the **rice bodies pressed out** and the cavity **washed out**. In extreme cases the synovial membrane or **sheath** must be completely **removed**.

Tuberculosis of the Shoulder.—For tuberculosis of the shoulder, elbow and wrist, see Treatment under Deformities of these joints.

ETIOLOGY.—See under the other joint diseases.

SYMPTOMATOLOGY.—Pain, tenderness, atrophy and limitation of motion are noted. The onset is insidious and the disease is chronic. There may be an abscess as in disease of the other joints.

TREATMENT.—In tuberculosis of the shoulder, the best position for **fixation** during the treatment is with the arm abducted 45 degrees. The general treatment is the same as that for any tuberculous joint.

PATHOLOGY.—See under disease of the other joints.

Tuberculosis of the Elbow, Wrist and Ankle.—**ETIOLOGY.**—See under disease of the other joints.

SYMPTOMATOLOGY.—There may be pain and tenderness. There is limitation of motion, chiefly of extension and later of flexion, supination and pronation. There is swelling of the joint, with atrophy of the

muscles. A tuberculous abscess may complicate the condition, as in disease of the other joints.

TREATMENT.—In tuberculosis of the elbow the best position for fixation is with the elbow at right angles and the forearm very slightly pronated.



FIG. 46.—ARTHROITIS DEFORMANS.

In tuberculosis of the small bones of the wrist and foot, if the disease does not subside markedly after prolonged fixation, an **excision** of the focus is usually followed by relief. In disease of the wrist, when an excision is necessary a complete excision of all of the bones of the wrist gives a much better result than excising one diseased bone only.

PATHOLOGY.—See under other joint diseases.

ARTHRITIS OF THE JOINTS

Arthritis—Osteo-arthritis—Arthritis Deformans.—The terminology used in dealing with the various forms of arthritis has never been definite enough to be helpful, unless it is supplemented by a description of the disease. The physician will find that the nomenclature is used differ-

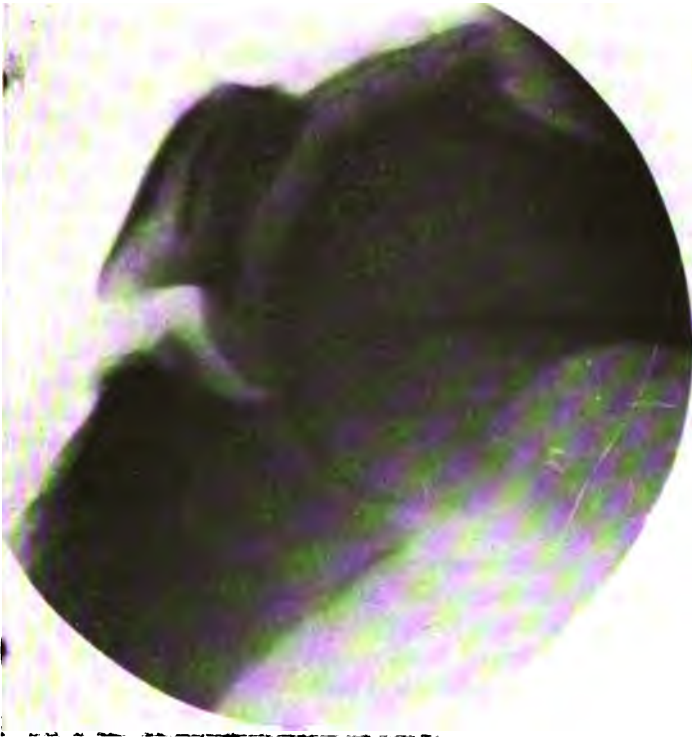


FIG. 47.—ARTHRITIS DEFORMANS, SHOWING INVOLVEMENT OF THE KNEE.

ently by almost every writer. It is important to distinguish clinically between certain forms of arthritis, and it is with this in view that the author will describe the following conditions, using the nomenclature approved by Dr. E. H. Bradford, Professor of Orthopedic Surgery at Harvard University Medical School. Dr. Goldthwait's clinical classifications, whatever their faults, are the most satisfactory for distinguishing the types present in various individuals. Dr. Edward H. Nichol's pathological research on the arthritic joints has helped the author to classify and treat the cases with increasing satisfaction. The cases

observed in large clinics will often include more than one type, occurring in the same individual (Figs. 46 and 47). It is possible for all types to be present in one case, but each form will be found to have a separate history, and will act in the main according to the type to which it belongs. The following classification will be found to be fairly simple and useful for the clinician, although no classification offered so far has been altogether satisfactory.

Degenerative or Atrophic Arthritis.—**ETIOLOGY.**—This condition is polyarthritic, affecting first the small joints, fingers, wrist, elbows, knees, tarsus, shoulder, jaw and spine; the hips are rarely involved. This form of arthritis occurs in young adult women more frequently than in men, only the highly civilized—those living a high-strung nervous life—being usually affected.

Grief, nervous shock, physical and mental strain, are important factors. The daily strain upon teachers of caring for forty or fifty children in one room, while teaching at the same time, poverty, responsibility, the physical strain of household duties, a nervous temperament with poor physical strength, all predispose to the disease.

SYMPTOMATOLOGY.—Pain is not severe, there is no "soreness" as in the infectious type of arthritis. At first there is a boggy swelling about the joint, later atrophy; this is noticed characteristically in the hands, where the atrophy between the metacarpals is characteristic. There is fixation, due later to erosion, but in the earlier stages due to habit of position and to degenerative changes eliminating the elasticity and range of motion of the joint. There may be subluxation at the knee, and joint motion may be jerky, due to erosion, and to lack of elasticity in the tissues. There is no local redness, although there may be local tenderness, slight local temperature, and slow progressive disability and deformity. Any constitutional disturbance is due to inactivity. Malnutrition and poor circulation are early noticed, also dry skin, dry nails, general debility, constant joint discomfort, low pulse and absence of fever; the hemoglobin is usually high until the debility is marked; there is very little change in the blood.

TREATMENT.—The treatment consists in attention to the general nutrition, to increase in the food, and to the local circulation. Indigestion may make it necessary to feed the patient often with small amounts of nourishing food. The deformities are gradually straightened by splints and plasters. One should avoid antirheumatic remedies, as well as salicylates and iodids. Asperin helps some cases, also massage between the joints, heat and Bier's hyperemia treatment. A warm climate in winter is often advisable.

PATHOLOGY.—All of the joint structures are involved—cartilage, bone synovia, and the synovial fluid. The synovial membrane is affected early and thickens. The villi tips are swollen, and there is a red-cell infiltration and a reddish-purple appearance due to passive congestion. Following this, fibrous tissue formation replaces the passive congestion. Vascularity becomes less and less, and degenerative changes are marked.

The cartilage is dull in color, and there are small, erosive, degenerative areas with no inflammation about the erosion. Bony changes come late. The intratrabecular fat is increased, and the trabeculae are diminished in number; later rarefaction of the bone and obliteration of the cartilage take place; there is no increase in the joint fluid. Bone and cartilage deposits appear in the villi of the synovia.

Proliferative or Hypertrophic Osteo-arthritis.—**ETIOLOGY.**—Trauma and exposure to extremes of temperature or humidity are prominent predisposing factors. The disease is found in firemen, teamsters, refrigerator plant workers, longshoremen, heavy load workers, and in conjunction with arteriosclerosis, in elderly people. Spine lesions are more common in this latter variety. Involvement of the elbow is found in baseball players.

SYMPTOMATOLOGY.—There is no constitutional disturbance. When the condition is first discovered there are no marked changes visible on the x-ray plate. Pain is usually the result of slight or severe trauma or of motion out of proportion to the range of the joint; as the pain disappears a bony enlargement is noted, also deformity and lameness. Digestive disturbance, flatulence, and constipation are frequent.

The hip and knee cause more disability than do the other parts. The lipping is observed at the edges of the joints of the knee, spine, feet, patella, and hip (*morbis coxae seniles*). There is limited motion, due to the proliferation of bone about the joint; later deformities occur in all the affected joints.

TREATMENT.—Treatment consists in **local heat** and in **correcting mechanical faults** in the use of the joints, to prevent deformity. Attention must be paid to **digestion** and to the condition of **bowels and kidney**. **Protection** and **rest** during the acute symptoms, Bier's **hyperemia treatment**, careful **massage** above and below the joint, avoiding the joint, **sodium phosphate** and **olive oil internally** are important. **Plaster of Paris bandages** are indicated when there is much pain.

PATHOLOGY.—In the young there is thickening and infiltration about the joint ligaments, with very few joint and cartilage manifestations. In middle life the cartilage and osseous tissue are affected; there is little synovial change; the cartilage proliferates. Thickening occurs on the dorsum of the terminal phalangeal joints; when the disease is pronounced there is a marked lipping and osseous spurs about the joint, noticed especially at the knee, the spine and the hip. The bone is normal at first; later there is a mechanical erosion due to the spurs. There are no inflammatory deposits in and about the erosions.

The lesions are slow and require years for their formation.

Infectious Arthritis (Nontuberculous).—**ETIOLOGY.**—This type of arthritis is due to bacteria or their toxic products. It is a systemic toxemia with joint infection. There may be almost no constitutional symptoms. Disease of the ear, throat, teeth, eyes, heart, glands, abdominal organs, intestine, pelvic organs, prostate, seminal vesicles, respiratory

system, and epidemic infections, may cause the condition. Usually, but not always, the onset is sudden. The joint involvement may follow in a few days or somewhat later. The condition is usually polyarticular; the original joint may clear up early in the disease.

SYMPTOMATOLOGY.—There is swelling, pain, limitation of motion, loss of function, and spasm followed by deformity. Often there is general glandular and splenic enlargement. Secondary anemia, slight temperature, high pulse, loss of flesh and loss of sleep, are noted.

TREATMENT.—All sources of infection should be sought for and eliminated. The local resistance should be increased. The inflammation may be reduced by heat, local applications, and fixation to eliminate spasm. Suppurative cases will require operation. All abscesses should be freely drained. Manipulation to relieve stiffness will give good results only when the adhesions are not too extensive. Deformity in flexion with joint motion is often best treated by osteotomy (see Treatment of Deformities). Braces are often very helpful in correcting deformity and in fixing the joint while it is sensitive. As the acute symptoms subside the circulation and muscle tone should be improved by massage, omitting the joints, and by the judicious use of exercises.

Pain is best relieved by heat, fixation and rest, and in suppurative cases by drainage. Bodily strength should be increased by hygienic measures and diet, and by tonics after the acute stage is over.

Antitoxins and vaccines are usually of doubtful value; in some instances they have helped greatly. It should be remembered that an osteomyelitis in the vicinity of a joint may be mistaken for an infectious arthritis.

Acute Arthritis in Infancy.—Acute arthritis in infancy is an acute infectious process in the hip epiphysis; the process is destructive and the hip usually dislocates. A small abscess discharges in the vicinity of the trochanter, usually posterior to it. An examination will show a dislocation with complete destruction or separation of the head or, in some cases, a dislocation only. The condition is usually secondary to some infectious disease such as scarlet fever, inflammation of the middle ear, or pneumonia. Very often the local process is not noticed until the child recovers from the original infection; the hip is then found to be dislocated. It is an infection of infancy.

When the head of the joint is not destroyed or only partially so, the hip may be treated in the same way as for a congenital dislocation. The acute symptoms are: acute pain, swelling, tenderness, local heat, spasm, and high temperature. The constitutional symptoms are often attributed to the original disease and the local condition not noticed. As soon as the condition is recognized it should be operated upon. Dislocation of the hip has often been prevented in this way.

Gonorrheal Arthritis.—Gonorrheal arthritis is an inflammation of the joint following gonorrheal infection. In many cases the original gonorrheal infection has disappeared and the joint condition has followed a remote or obscure latent focus, for instance, in the pelvis or seminal vesicles.

The condition may affect one or many joints.

SYMPTOMATOLOGY.—There is usually pain, swelling, local heat, disability, spasm, limited motion, and swelling of the capsule. In subacute cases there is discomfort, weakness, swelling and disability. When the seminal vesicles are involved there may be no external evidence of disease.



FIG. 48.—HIP FLEXION DEFORMITY. Poliomyelitis.

TREATMENT.—The **drainage** of these vesicles is usually followed by a very satisfactory relief from all joint inflammation. When the joint infection is purulent instead of serous or serofibrinous in form, thorough **drainage** and **washing out of the joint** is indicated, but even then the joint is apt to be destroyed. In this form of arthritis there is often very extensive destruction of the cartilage, followed by bony ankylosis. It is important to waste no time in **removing the original focus** when it can be located.

JOINT DEFORMITIES

Deformities may be due to trauma, to static conditions, to muscular contracture, to muscle weakness, to atrophy, or to paralysis. Prenatal conditions and disease also cause deformity. When no disease remains,



FIG. 49.—COXA VARA.

or when the condition is not due to disease, the deformity should be corrected as early in life as possible.

Deformities of the Hip

Hip Flexion.—It is difficult and unsatisfactory to stretch the hip flexors when they are markedly short and when the hip has been held flexed for any length of time (Fig. 48).

TREATMENT.—Hip flexion, due to a pathological condition of the soft tissues, may be corrected by **operation** to lengthen the hip flexors (Soutter operation).

Hip flexion due to old disease or to fracture may be corrected by an oblique **osteotomy** just below the trochanter (Gant operation). The leg and pelvis should be held in an overcorrected position for six weeks. The results are very satisfactory.



FIG. 50.—COXA VALGA.

Lordosis.—This deformity is often very painful and is frequently due to the stiffening of the hip in a flexed and adducted position. When this is the case the **deformity** should be **corrected** and the back will flatten and the pain be relieved. Occasionally lordosis is due to paralysis of some of the trunk-muscles, to faulty attitude in standing and sitting, to scoliosis, or to bony anomaly or deformity.

Coxa Vara.—Coxa vara consists in the decreasing of the angle of the neck of the femur, the head being lower than the top of the tro-

chanter (Fig. 48). It may be due to fracture or to softening of the neck, as in rickets, and arthritis deformans. When a coxa vara exists the motion in abduction is more or less limited, depending upon the degree of the deformity. In extreme cases there is no motion in abduction.

TREATMENT.—Cases may be relieved entirely by an oblique **osteotomy** just below the great trochanter, the leg being placed in an abducted position, slightly hyperextended, and held there until the bone is solidly united. This takes from five to six weeks.



FIG. 51.—SUBLUXATION OF THE KNEE.

Coxa Valga.—Coxa valga is not as common as is the reverse deformity, coxa vara. The angle of the neck of the femur is increased, the head being higher than normal (Fig. 50). Usually the condition requires no treatment unless it accompanies a dislocation.

Deformity of the Knee

Knee-flexion.—**TREATMENT.**—Knee-flexion which has existed for any great length of time is often difficult to correct and can rarely be overcome by manipulation. A well-padded plaster of Paris bandage may be



FIG. 52.—CONGENITAL CLUB-FOOT. (Equinovarus.)

applied, and a slit cut in the plaster across the popliteal space. Small wedges are put in the slit, spreading the plaster apart. One or two pieces of wood one-eighth of an inch thick are added each day, or thinner ones if these cause pain. A flexed knee may be straightened in from three to six weeks in this way, the plaster being changed every five to ten days, depending upon the individual case. If this method is not successful, an **osteotomy** at the level of the adductor tubercle will allow the knee to be straightened and prevent the joint from being injured by the trauma of manipulation. After correction is established, a caliper

VOL. VI—33.

splint is used for part of each day for from six to twelve months, depending upon the tendency to slight flexion.

Subluxation of the knee, depending upon the duration, is corrected by a **genuclast** (Fig. 51). If the joint action is good, it may be better to correct the flexion as described above, by an osteotomy, and not to attempt to correct the subluxation. The surgeon will have to decide in each individual case.

Deformities of the Ankle and Feet

Postural Conditions of the Feet.—**ETIOLOGY.**—Deformity is caused by a disproportion between the weight to be borne and the muscular power which bears it. Weakness of the muscles of the leg and feet caused by footwear which cramps the front of the foot, and by faulty attitudes in standing and walking, also weakness following trauma or illness, are the chief exciting causes.

SYMPTOMATOLOGY.—Deformity, pain, tenderness, muscular spasm, are noted. Stiffness and ungraceful gait are noted.

TREATMENT.—Relief may be obtained from the **replacement of displaced tarsal bones**, **removal of strains**, the overcoming of midtarsal stiffness and restoration of the muscular strength needed in sustaining the body weight, by means of **exercises**, and **proper shoes**.

Equinovarus (Club-foot).—**Varus.**—This is a deformity characterized by adduction of the front of the foot, depression of the front of the foot, and prominence of the cuboid bone. In extreme cases the patient walks on the cuboid and external malleolus, no weight being borne on the heel and sole of the foot (Fig. 52).

TREATMENT.—In infants, gentle **manipulation** may be begun about the eighth week and continued as the child grows older, if the deformity is considerable.

The deformity may be corrected by manipulation, by **tenotomies** and by manipulation, by **lengthening the ligaments** at the inner malleolus (Ober operation), by **removing a wedge of bone** and, in paralytic cases, by manipulation, tenotomies and **tendon transplantation** (Fig. 53).

In view of the better modern understanding of this deformity the **Phelps operation** for club-foot should be **avoided**, as the other operative measures are preferable.

Talipes varus is an inward twist of the front of the foot and prominence of the cuboid bone. When the foot is in an extreme **varus** position the plantar surface points to the side and the patient walks on the cuboid and malleolus.

Pes Cavus.—*Pes cavus* designates a hollow, contracted foot (Fig. 54). It may be inherited or may be due to high heels, or to excessive use of the calf muscles, as in the case of dancers, or to paralysis or muscle contracture.

The condition may be accompanied by some equinus and is probably due to a slight transient paralysis of the anterior groups of leg muscles

and to contraction of the posterior group, or it may result from a sprain or fracture above the ankle. There are no symptoms, unless the equinus is exaggerated. The patient may require specially fitted shoes. There may be some pain and limitation of dorsal flexion, due to contraction of the plantar fascia.

TREATMENT.—Many operations have been suggested for this condition. If there is pain it is usually due to lack of dorsal motion of the foot,



FIG. 53.—CLUB-FOOT. Postoperative position.

the equinus or to the claw-foot or hammer-toe condition. Pain will be relieved by the application of appropriate treatment for these deformities.

Equinus.—Equinus denotes a position of the foot with the ball of the foot pointing down. The patient is unable to reach the ground with his heel.

ETIOLOGY.—The condition is due to prolonged use of high heels, to faulty position following trauma, to prolonged bed treatment, or to muscle contracture, rheumatism, arthritis deformans, disease, inflammation or paralysis.

TREATMENT.—Equinus due to shortness of the tendo achillis may be corrected by **tenotomy** and **manipulation** followed by a **protective plaster** for six weeks. During the last week the patient may be allowed to walk, with the plaster in place. Equinus due to bony deformity will have to be corrected by osteotomy or by **ostectomy** and manipulation.

Equinovalgus—Valgus.—*Equinovalgus* is characterized by abduction and pronation of the foot (Fig. 55). The deformity may be corrected in the same way as club-foot. It should be **overcorrected** and the overcorrected position maintained for from six to eight weeks until locomotion is reestablished.



FIG. 54.—PARALYTIC FEET. (Pes cavus.)

Valgus is an abducted position of the foot with a low position of the scaphoid bone. It may be due to congenital deformity, weakness or paralysis of the tibials or to contraction of the peronei, or to both.

Flat-foot—Valgus.—**TREATMENT.**—Flat-foot, when slight, may be corrected by a good **broad shoe** with a straight inner line, and by **exercises** to strengthen the muscles of the foot and to establish a proper attitude in standing. This treatment will be effective if persevered in. **Plates and pads** should be used for **as short a time as possible** or not at all in mild cases.

When the condition is extreme, **manipulation** and forcible **correction** under ether will sometimes be sufficient to correct deformity. The foot is put in **plaster** until the patient can walk without pain. In some cases a **wedge** must be **removed** from the **scaphoid bone**, in order to allow full correction for the deformity.

Calcaneus — Calcaneovarus — Calcaneovalgus.—*Talipes calcaneus* consists in dorsiflexion of the foot with prominence of the heel. It is usually due to a contraction of the anterior muscles, or to relaxation or paralysis of the posterior muscles, or to both. It may be due to congenital malformation.

Calcaneovarus consists in dorsiflexion of the foot with adduction of the front of the foot and a low position of the cuboid bone. It may be due to a combination of the same causes which produce varus and calcaneus.



FIG. 55.—POLIOMYELITIS, WITH EQUINOVALGUS DEFORMITY. Note the shortened extensors of the toes.

Calcaneovalgus consists in dorsiflexion of the foot with a low position of the scaphoid bone, and tilting upward of the forward end of the os calcis. It is usually due to congenital malformation, to faulty growth of the bones, or to weakness or paralysis of the tibials, and rigidity or contraction of the peronei.

Flail-ankle.—In the condition of loose ankle and loose foot, the position is inward, outward, anteroposterior or all combined. It is due to a relaxation of the ligaments and muscles on one or both sides, or anteriorly or posteriorly, or on all sides, following trauma or nerve-muscle-paralysis. The common form of flail-ankle is that seen in poliomyelitis.

TREATMENT.—In certain anteroposterior flail conditions, when the displacement is lateral, and the muscles on the other side are normal, a muscle or tendon **transplantation** may be performed to balance the ankle. In some instances the insertion of **silk ligaments**, or **tendon fixation**, are advisable, in others, **astragalectomy**, with displacement of the foot backward may be preferable. This last operation in extreme flail conditions gives the most satisfactory results for weight-bearing without stiffness, and renders a brace unnecessary.

Deformities of the Wrist and Hand

Madelung's Deformity of the Wrist.—This is a subluxation of the wrist forward and generally toward the radial side. The ulna and radius are more widely separated than usual and the radius is usually curved. The condition is often bilateral.

ETIOLOGY.—The condition occurs usually in adolescence. The predisposing factors are relaxation of the ligaments, stretching of the muscles, previous rachitic deformity and sometimes injury.

SYMPTOMATOLOGY.—There is a weakness of the wrist, limitation of motion, chiefly of hyperextension, but sometimes also, of pronation, and supination. Occasionally pain is present.

TREATMENT.—The treatment consists in **exercises**, **hyperextension**, **supports** and **massage**. Occasionally **osteotomy** of the radius is indicated, depending upon the amount of deformity and disability present.

Dupuytren's Contraction.—This is a deformity due to contraction of the palmar fascia, affecting also the fingers. These become flexed to a lesser or greater degree.

The *etiology* is not known. Arthritis, usually of the proliferative or degenerative type, is generally present to a greater or lesser degree in all cases.

The condition may be bilateral. There is thickening of the palmar fascia, or of the tendon-sheath or bone, and general contraction. Occasionally pain is present.

TREATMENT.—The treatment consists in multiple **incision** of the bands, or, if possible, complete **removal of the fascia**, followed by systematic and gentle **overstretching** in order to maintain the overcorrection obtained at the time of operation.

Congenital Club-hand.—There may be distortion in any direction. The condition may be due to constant pressure *in utero* without other abnormalities, or it may be associated with club-foot, absence of the radius or of the ulna (Fig. 56). The most important form is that associated with defective radius. In these cases the ulna is short and bent and often makes a right angle with the hand. There is also defective formation of muscles and ligaments. When there is absence of one of the long bones one or more fingers are absent on that side of the hand. Other deformities of the hand sometimes accompany club-hand, such as webbed fingers, deformity of the fingers or partly united fingers.

TREATMENT.—When no other deformity is present, **manipulation** and **fixation in plaster** may be sufficient. In other types, **tenotomies**, **tendon transplantation** and **osteotomies** are necessary, or, when one bone only is present, this is **split**, the carpal bones shaped to fit between, and in this way the hand is held straight so that the finger-tendons may function.



FIG. 56.—CLUB-HAND WITH ABSENCE OF THE RADIUS.

OTHER PATHOLOGICAL CONDITIONS OF THE JOINTS

Limited Motion and Deformity of the Arms.—**TREATMENT.**—This condition is corrected by **manipulation** or **osteotomy**, and maintained in paralytic cases by **tendon transplantation** and **braces**. Knock-elbow is corrected by osteotomy, stiffness of the elbow by **plastic operation** on that joint. This will reestablish the use of the joint, giving full flexion and extension to within 5 or 10 degrees of a straight line.

At the shoulder, a **partial excision** will help to correct the limited motion, provided the muscles are good.

Limited motion and stiffness of the wrist may be relieved by an excision. In rheumatic cases, operations for reëstablishing motion are not usually advisable.

Ankylosis.—This consists in the chronic fixation of a joint in a certain position. It may be a partial fixation, limiting the motion



FIG. 57.—ANKYLOSIS OF THE HIP.

slightly or almost entirely, or it may be complete (Fig. 57). It is due to trauma, or to an inflammatory process within or without the joint, resulting in the formation of fibrous adhesions, or sometimes of bony adhesions, limiting the motion about the joint. The best way to prevent ankylosis is by proper treatment of the diseases of the joint, by **passive motion, baking and Bier's hyperemia treatment**. If ankylosis seems inevitable it should be changed to a position which gives the greatest function to the joint.

TREATMENT.—Forcible correction is usually inadvisable, but the indications depend upon which joint is involved, and upon the type of ankylosis. Tuberculous joints should not be manipulated. After the disease is completely cured the limb may be straightened by an osteotomy done in the healthy bone above or below the site of the old disease. If the ankylosis is fibrous, repeated manipulations in recent cases are sometimes useful. If it is bony, osteotomy is indicated. When the ankylosis is due to trauma or to old disease, which has subsided long ago, but not to tuberculosis, incision or arthroplasty or other plastic operations are advisable in certain cases involving the shoulder, elbow, wrist, hip or ankle. The knee is not a favorable joint for arthroplasty.

Semilunar Cartilage Displacement.—This condition is usually traumatic, and the internal cartilage is the one most often involved.

SYMPTOMATOLOGY.—The symptoms are sudden pain, inability to extend the leg fully, and swelling, with often a palpable protrusion of the cartilage. It is usually followed by a synovitis. One attack predisposes to succeeding attacks and in time the cartilage may be entirely loose and form a foreign body in the joint.

TREATMENT.—The immediate treatment consists in reduction. This is accomplished by flexing the leg as much as possible, by abduction of the femur, rotation inward and sudden extension. A plaster of Paris cast is used after the swelling has subsided. In chronic cases the treatment consists in opening the joint and removing the cartilage,

Relapses are often due to lack of recognition of the condition when it first occurs after the first attack, or to too short immobilization. It is important to allow time for the cartilage to adhere. When the swelling has subsided the plaster cast is continued and the patient allowed to walk, with a straight knee. Immobilization is continued for five weeks. Only slight motions in flexion are allowed for the following two weeks.

Prepatellar Bursitis (Housemaid's Knee).—This condition consists in an enlargement and an effusion into the bursa over the patella. The symptoms are pain, swelling, and discomfort in the region of the knee. The swelling is localized, and there is definite fluctuation. There may be suppuration. One attack predisposes to others.

TREATMENT.—The treatment consists of counterirritation, hot applications, rest and fixation. In severe cases the sac should be excised.

Loose Bodies in the Knee-joint (Joint-mice).—These may consist of bits of bone, cartilage, or fibrin. They are apt to be found in conjunction with synovial tuberculosis and arthritis deformans. They are freely movable, and cause no symptoms unless they become caught between the bony surfaces, in which case there is sudden, sharp pain followed by an effusion into the joint. The symptoms may recur.

TREATMENT.—The condition is treated by removal of the loose bodies. Whenever possible, they should be counted and located and the extent of the excursion of each body noted before operation.

Tenosynovitis.—Tenosynovitis of the wrist or tendo achillis is usually due to strain, to pressure, or to both. There is often exquisite tenderness and pain with motion, and loss of power.

TREATMENT.—In cases of long standing, mild **counterirritation**, **immobilization** and **protection** from all pressure on and in the neighborhood of the sheath are important. The shoe should be cut away behind for two inches at least, and loose leather used to cover the gap.

PATHOLOGY.—In some cases of long standing a few or many calcified deposits are found in the sheath. They may be small or large and long.

Acute Synovitis.—**SYMPTOMATOLOGY.**—The signs and symptoms are: local heat, thickened capsule, fluid, spasm of the muscles, slight flexion of the knee, and limitation of motion.

TREATMENT.—The treatment should consist of **splints** or **plaster**, in the severe cases of the application of **ice bags**. Absorption of the fluid is favored by the use of the leg without the removal of the splint. When the condition is slight, **adhesive strapping** to limit the motion in flexion is of value, with **rest** for from three to five days, followed by the use of the leg without removal of the adhesive bandage. **Rubber anklets**, **knee-caps**, **wristlets** and **elbow supporters** are apt to interfere with the circulation and repair. Where it is necessary to use them, they should be discontinued as soon as possible. **Exercises** and **massage** are indicated after the acute symptoms have subsided.

Intermittent Synovitis with Effusion.—The condition exists without apparent cause, occurring at regular intervals every two, three or four weeks. There is discomfort and swelling, which disappears after from three to five days. Digestive disturbances sometimes accompany the condition. It is probably a trophic neurosis.

TREATMENT.—The treatment consists of general hygiene, regular **exercises** and **habits** of life, **care** of the **bowels** and digestion, and the administration of **thymus extract**.

Charcot's Disease.—**ETIOLOGY.**—This form of joint disease may be associated with locomotor ataxia, syringomyelia, Pott's disease, acute myelitis, injuries of the peripheral nerves, etc. The joints are usually affected in the following order: knee, hip, shoulder, tarsus, elbow, ankle, wrist, jaw and spine.

SYMPTOMATOLOGY.—This condition occurs in syphilitic and tabetic patients. There is a degeneration of the cartilage and of the underlying bone, with irregular formation of cartilage about the joint. Thickening of the synovial membrane takes place. With the condition there is often a looseness about the joint, the knee, hip or ankle. There is marked swelling and effusion and often considerable deformity. No local pain nor sensitiveness are noted. There is usually more or less weakness. The process often progresses until there is actual dislocation.

TREATMENT.—Very often no treatment is necessary when the condition is slight, but in the case of the joints of the leg, **apparatus** is often necessary to support the joint and prevent dislocation.

PATHOLOGY.—The pathology is much the same as that found in arthritis deformans. The activity of formation is less, while the destructive process becomes very rapid.

Gout.—**SYMPTOMATOLOGY.**—Patients with gout come to the orthopedic surgeon because of the pain and swelling about the joints. It is a

medical disease. There are acute inflammatory processes with chronic changes about the joints, and characteristic deposits of sodium urate in the cartilage surrounding them. Before the joints are enlarged there may be infrequent twinges of pain. An *x*-ray will often show a thinning of the middle of the shaft of the metacarpal or metatarsal bones early in the condition (Fig. 58). The pain first appears in the feet and hands, especially in the great toe joints. These are hot and tender, and an irregular deformity of the small joints occurs. There may be three or four severe attacks a year and sinuses may develop at the joints.

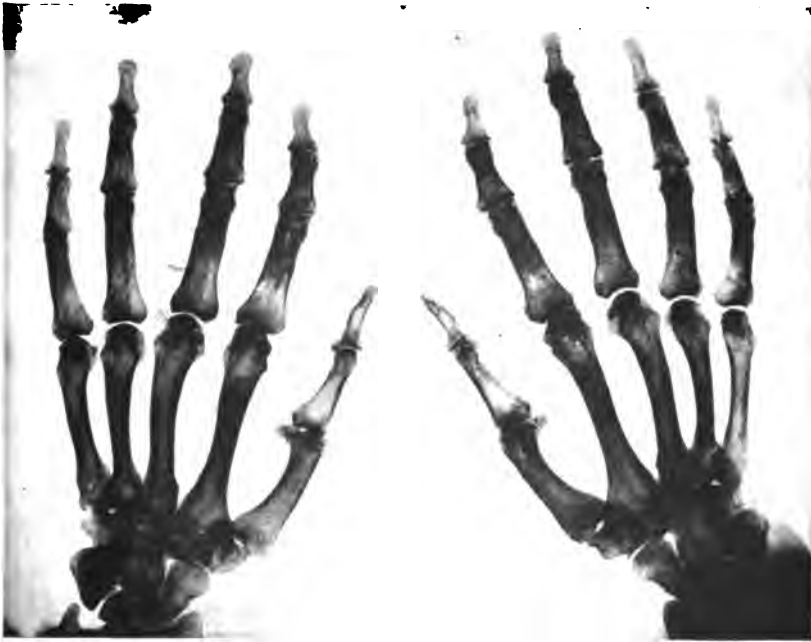


FIG. 58.—GOUT. The thinning of the proximal phalanges is shown near their distal ends.

TREATMENT.—Treatment consists in **rest in bed, warm applications and soaks** to allay the inflammation. **Cold** is sometimes more acceptable than heat. Digestive symptoms should be treated. Doses of **calcium** and **salicylate** will help to relieve the pain. Eight or nine glasses of liquids should be taken daily.

Scapula Crepitus.—Scapula crepitus is the name applied to the condition of grating produced by motions of the scapula. The affected side is usually tender at certain points. There is, as a rule, a small bursa or gland, or a dry condition of the muscle. Bony irregularities are sometimes present.

TREATMENT.—When there is much pain, **heat, gentle massage** and **exercises** will relieve the pain. In some instances **immobilization** is necessary.

Sprained Ankle.—A sprain of the ankle is generally caused by suddenly turning the foot inward or outward with sufficient force to cause injury. The injury may consist in the stretching or rupture of tendons, tendon-sheaths, capsules, muscle-fibers, in conjunction with injury to



FIG. 59.—ISCHEMIC PARALYSIS.

the synovial membrane. There may be effusion or hemorrhage into the joint. An *x-ray* photograph should always be taken, in order to exclude the suspicion of fracture.

SYMPTOMATOLOGY.—The symptoms are severe pain, throbbing, swelling, heat and sometimes discoloration.

TREATMENT.—The treatment consists in **immobilization** and **rest** with **adhesive strapping** or, in severe cases, in the adjustment of a **light plaster** with the foot in slight dorsal flexion.

Subdeltoid Bursitis.—There is sometimes an inflammation of the bursa lying underneath the deltoid muscles.

SYMPTOMATOLOGY.—The symptoms are pain, tenderness, and limited motion, chiefly in abduction and rotation. Sudden motions are accompanied by sudden, sharp pain. There is no involvement of the joint. Gradually an atrophy of the shoulder-muscles results. The cause is often trauma, but at other times the etiology is obscure.

TREATMENT.—The treatment in the acute stage includes **rest, heat and counterirritation, and fixation**. Later **massage and graduated exercises** are indicated. In obstinate cases **operation** for the **removal of the bursa** is sometimes necessary.

Ischemic Paralysis—Contraction.—This condition is observed following the application of apparatus for fractures about the elbow. There is prolonged constriction, due to the pressure of the apparatus. This results in swelling, discoloration, numbness, and later paralysis and contracture (Fig. 59). There is fibrous degeneration of the flexor muscles resisting extension. The fingers and wrist are flexed and sensation is often lost.

TREATMENT.—**Prevention** of the deformity is important in fractures of the elbow. The apparatus should be frequently examined and the patient should move the fingers early in the treatment.

When paralysis occurs the fingers and hand should be put in **hyperextension**. **Exercises and massage** should be started as early as possible. The contractures have been relieved in some cases by **shortening of the bones** of the forearm, followed by **muscle-reduction**.

SECTION VII

DISEASES OF THE MUSCLES

CHAPTER I

INFLAMMATORY DISEASE OF THE SKELETAL MUSCLES

By C. F. HOOPER, M.D.

Etiology, p. 527—Symptomatology, p. 528—Differential diagnosis, p. 528.

Muscular rheumatism, p. 530:—Symptomatology, p. 530—Dermatomyositis, p. 536:—Etiology, p. 536; Symptomatology, p. 536; Treatment, p. 541; Pathology, p. 542—Gout, p. 543—Myositis fibrosa, p. 543—Syphilitic myositis, p. 544—Trichinosis, p. 545—Gonorrheal myositis, p. 545—Muscular atrophy and joint diseases, p. 545.

Literature on disease of the skeletal muscles is not abundant. If we consider the volume of the muscles, their function, blood supply, and exposure to injury from external and internal sources, we find the attention given the muscles in both clinical and pathological literature to be very meager. In fact the physician is prone to neglect the consideration of the skeletal muscles. There seems to be a general assumption that muscles are immune from disease. This criticism is based upon: the common failure to consider the abdominal muscles in patients who complain of abdominal pain, upon neglect of the neck and shoulder girth muscles when the patient complains of pain in this region; and also upon neglect of the lumbar and pelvic girth muscles when the complaint is of pain in the sacrolumbar and hip region.

Etiology.—On account of the free anastomosis of blood-vessels, there are not many instances of gross lesions of the muscles from ischemia and infarcts, although in the absence of a proper examination small infarcts of the muscles may escape attention. Metastatic infections of the muscles are commonly located near the junction of the muscle with its tendon or aponeurosis, and for this reason a disease of the muscle may be mistaken for disease of a neighboring joint or tendon sheath. Joints, ligaments, tendons, and bursæ are much more frequent sites of disease than are the muscles, and on account of the predominance of these sources of pain, the muscles are quite neglected. Subjective pain from a muscle is not located with the same accuracy as is pain in superficial structures. Consequently the vague location may be very mis-

leading, and unless the muscles of the affected area are carefully examined, the pain is likely to be interpreted as originating from a nervous source.

Symptomatology.—EXAMINATION OF A MUSCLE.—There is nothing new to suggest in the examination of a muscle, except one point which has not been noted in any literature on the subject. Observations without comment have been made by several writers to the effect that patients suffering from several forms of myositis experienced little discomfort in walking, but that the muscles were painful to pressure and were very painful when they were stretched. One of the author's patients ruptured eight muscles in myositis of prolonged duration, but suffered very little pain when the ruptures occurred; he stated that there was little pain preceding the ruptures.

Unlike most other structures which are tested for the seat of pain, functional employment of a muscle is painless when the seat of the disease lies within the muscular sheath. Perimyositis may cause pain when the muscle is activated, but myositis causes pain only when the part is palpated or when the muscle is stretched. If this point is neglected, myositis will be overlooked. It is the general practice to employ a structure functionally, as a test for pain; if exercise of the normal function is painless, the suspected structure is eliminated as a source of pain. It is distortion of the affected area which causes pain when pressure is applied. If it is applied equally in all directions, as hydrostatic or pneumatic pressure is transmitted, it will not cause pain. This is the case when a muscle is activated. The contents of the muscle-sheath constitute a semi-liquid mass, and when the muscle is contracted there is an increase of intramuscular pressure; but the pressure is equally transmitted in all directions, and causes no distortion when an inflamed area occupies a small part of the muscle, nor when it extends throughout the muscle, as in some cases of trichinosis. When pressure is applied to an area of myositis, or when the muscle is stretched, there is distortion of the affected area, so that the conditions are attended by severe pain. If stretching a muscle causes pain, it should be carefully palpated for sensitive areas and for palpable welts or nodules.

Differential Diagnosis.—It is true that a differential diagnosis of gout, rheumatism, exposure to cold and moisture, and other sources of metastatic infection of the muscle, is very unsatisfactory. Very often one cannot palpate any swelling or area of induration in the muscle, but the point of sharply defined tenderness can be very clearly located, and by the employment of several tests for the location of intramuscular disease the muscle may be satisfactorily proved to be the source of pain, although the etiology of the painful point often remains in doubt.

A woman, about fifty years of age, was recently admitted to the wards at Lakeside Hospital, suffering from a painful affection of the upper right abdomen, on account of which surgical exploration of the abdomen had been advised. It was for this reason that she came to

the hospital for further advice. The secretory and motor functions of the stomach were found to be perfectly normal, and there was nothing in the history nor in the findings which indicated that the gall-bladder or the gall-duct was at fault. The patient complained of pain, which she described as being vaguely located over the upper right half of the abdomen. On palpation a point was discovered in the external half of the right rectus muscle, on a level with the seventh costal cartilage, which was exquisitely sensitive to pressure. If this point was palpated when the muscles were activated, the tenderness was greater than was the case when the muscles were relaxed. The tender area was not larger than the berry of a man's thumb. There was no palpable induration or swelling. If the patient made an effort to sit up, no pain attended the effort. However, when a firm bolster was placed under the small of her back so that she was put into the position of lordosis, and the rectus abdominis was stretched, she complained of severe pain, which was referred to the upper right abdomen.

When a painful point is located in the abdominal muscles, and differentiation between the abdominal muscle and the abdominal peritoneum is to be made, tests of pallesthesia and perception of cold may be employed in making the differentiation. For instance, as in the case just described, if the palpably located tenderness has originated from localized peritonitis in the abdominal wall, one will find a small area over the site of the tenderness, perhaps not more than an inch square, over which the vibration of the tuning-fork will be much less keenly perceived than over a point on the symmetrically opposite side of the abdomen. Over this same area the perception of cold will also be greatly diminished. It is common to find over these areas complete loss of perception of the vibrations of the tuning-fork; in such cases even intense cold may not be perceived as cold. This area of dissociation of sensory percepts is not consistent with the distribution of the peripheral nerves, nor does it have any relation to segmental distribution from the spinal cord. The area is palpably defined and palpably located as the site of underlying peritoneal irritation. This dissociation of sensory percepts in the skin overlying an area of peritoneal irritation is of service in locating the site of an intra-abdominal source of pain when disturbances of the adnexa, appendix or gall-bladder, ulcer of the stomach, or invasion of any other circumscribed area of the peritoneum accompanies a lesion. The writer has always found that, when localized tenderness can be demonstrated within the abdominal muscles, the impairment of pallesthesia and perception of cold are not disturbed.

On several occasions the writer has seen patients with localized tender spots at the right of the rectus abdominis, over the site of the appendix. The tenderness on palpation was exquisite; the patients complained of the pain but were just as vague as to its location as most patients are who have pain from an intra-abdominal source. Several of these patients were rheumatic. One of the cases occurred during

the recent epidemic of influenza, and during army service in France 2 cases of this character were found among trench fever patients. In all these instances the question of appendicitis was raised, but it was possible, by asking the patient to contract the abdominal walls, to prove the tenderness to be in the abdominal wall and not in the abdominal cavity. Activation of the abdominal muscles was painless. Pressure on the sensitive area caused more pain when the muscles were activated than when they were relaxed. When the muscles were stretched the pain was severe.

Muscular Rheumatism.—This term is commonly treated with disdain by physicians, but is much used by the laity to describe their painful symptoms. The real truth lies somewhere between these extremes. The 2 cases described below are unusual on account of the severe muscular lesions, but they served the purpose of arousing the writer's interest in muscular lesions accompanying rheumatic arthritis, and as a result a number of cases of lesser severity were subsequently found which would certainly have been missed had not the severe examples been encountered.

SYMPTOMATOLOGY.—A woman, thirty-eight years of age, came to Lakeside Hospital in January, 1916. The patient dated her illness from an attack of "grip" six weeks before her entrance to the hospital. She had at that time been confined to her bed for two weeks. She had also suffered from cough, general malaise, sore throat and some joint pains. After recovery from her "grip," the patient began to have pain in the extremities and also in the vicinity of the jaw. She was unable to open her mouth on account of "pain in her jaw." The pains in her legs were rather indefinite in character, but she said that they started from the hips and went down even to the soles of her feet. In the arms the pain was mostly in the upper portion, but there was also some pain about the wrist, and the patient complained of inability to raise her arms above her shoulders in combing her hair.

When the patient was admitted to the hospital, she had an evening temperature of 100° F. (37.77° C.), with a pulse-rate between 70 and 80. There was no evidence of any involvement of the heart, or of the veins or arteries, and she was free from any demonstrable arthritis. Examination showed that the masseter muscles on both sides were very sensitive to touch. The right was distinctly more tender and thicker than the left. The floor of the mouth, and the muscles which move the tongue, were not involved, nor were the temporal muscles. The patient was able to bite without pain, but when she attempted to open her mouth, the movement was attended by very severe pain, which she referred to the temporomaxillary area. The pain could be definitely connected with passive stretching of the masseter muscle. The right triceps muscle in its lower half was distinctly indurated and sensitive, although the muscle was not paretic. Strong flexion of the forearm on the right side caused severe pain, which was located in the lower portion of the triceps. The right abductor indicis was indurated

throughout its entire extent and exquisitely sensitive to touch. None of the neighboring muscles of the thenar eminence were involved. Activation of the muscle caused only slight pain, but stretching of the muscle was exquisitely painful. All the intercostal and abdominal muscles were normal. The adductor magnus on the right side was palpable as a thickened mass from its origin at the ramus of the pubis to its insertion. It was painful on pressure and traction, but activation was not painful. In the plantar aspect of the right foot, over the adductor hallucis and over the flexor brevis digitorum and the flexor longus hallucis tendon, the area was sensitive to pressure and the muscles were sensitive to stretching. There was shortening of the flexor longus hallucis, so that the terminal phalanx of the toe was flexed, producing hammer-toe. This abnormality the patient said was due to an old process, quite similar to the present attack, which occurred five years ago. The flexor longus hallucis was not as painful as the other muscles. In the mid-portion of the belly of the right quadriceps extensor was an indurated area about three fingers in breadth which occupied the entire breadth of the muscle. This area was painful to pressure and when stretched, but active extension of the leg by the quadriceps was not painful. Over the right peroneal tendon, directly over the external malleolus, was a small nodular mass, about the size of an average peanut kernel, which was indurated and tender and felt like bone. It was apparently situated in the tendon-sheath. It was apparent at the upper border of the external annular ligament, and marked the portion of the belly of the peroneus tertius muscle where it joins the tendon. Plantar flexion of the tarsus caused extreme pain even with the toes in full extension.

From the clinical history of this patient, it could be definitely determined that she had had a joint inflammation during her first attack five years before, and it seemed very probable that we were dealing with a Payne-Poynton infection, although this point could be established only on the basis of clinical interpretation. There was no bacteriological evidence as to the character of the infection.

The second case of rheumatic myositis was in a man thirty-three years of age, who came to Lakeside Hospital in February, 1916. His illness had begun about fifteen years before while he was at school. He was seized with pain and swelling in his hands, knees and feet, and was forced to go home. This illness, which had such an acute onset, confined him to the house for about three years with arthritis. He said that during that time he had felt perfectly well with the exception of the pain in his joints. He also stated that nodules sometimes appeared about certain joints and under the skin of his legs. They would become quite sore and then entirely disappear. About thirteen years ago he lost the extensor power of both thumbs and of the third finger on both hands. The patient stated that this loss of power came on very suddenly and suggested the rupture of a muscle or tendon. Two years

ago the extensor power of his legs was temporarily lost. This occurred suddenly when he attempted to run.

Physical Findings.—The joints of the upper extremities were normal; there was no resistance or pain on motion; no atrophy was present



FIG. 1.—MUSCULAR RHEUMATISM. In this picture the patient was asked to hold his fingers and thumbs in an extended position. The photograph shows how the metacarpals of the thumbs are extended; the first and second phalanges remain in a partially flexed position. Both ring fingers are also in a partially flexed position at the metacarpal phalangeal joint.

in the arms, but in both hands the interossei were atrophied, and the wrist joints and metacarpal phalangeal joints showed some thickened remains of former inflammation. The extensor power of the proximal and terminal phalanges of both thumbs was gone. The extensor power

was preserved in the metacarpal of both thumbs, but, as shown in the accompanying photograph (Fig. 1), there was a complete loss of extension of the phalanges. In the lower extremities, as the photograph (Fig. 2) reveals, there was a fibrous strand in the lower third of both quadriceps extensors. This fibrous strand marks the position of a rupture of the quadriceps muscles, which occurred two years previously with moderate exercise. The photograph reveals the prominence at the lower end of the proximal portion of both quadriceps muscles. There



FIG. 2.—MUSCULAR RHEUMATISM. This picture shows the diminution in volume of the leg muscles, and the smooth, indurated and bronzed skin; the same characteristics of the skin and muscles of the forearm are apparent.

was also a palpable induration in the muscle in the lower third of the leg. The patient says that formerly there was marked thickening and tenderness at this site. The induration was bilateral, and on the right side the muscle could be identified as the extensor propius hallucis.

The accompanying photograph of the cervical region (Fig. 3) shows a prominence of the sternocleidomastoid muscle on the left side. This prominence was due to a fibrosis and consequent shortening of the lower third of the muscle, which was diseased during the first attack, fifteen years ago. For the present the disease has left fibrosis and shortening of the sternocleidomastoid of the left side, loss of power and extension of both phalanges of both thumbs, and the loss of the

534 INFLAMMATORY DISEASE OF SKELETAL MUSCLES

extensor power of the proximal phalanx of both right fingers. There was a fibrous union following the rupture of both quadriceps extensor



FIG. 3.—MUSCULAR RHEUMATISM. This picture shows the prominence of the sternocleidomastoid muscle on the left side. This prominence is due to shortening of the muscle from fibrous degeneration in its lower third.

muscles, and fibrous induration of the propius hallucis muscles of both sides.

In addition to the history of arthritis and the remains of extensive muscular disease which was incurred coincidently with the arthritis, the patient had traces of an old endocarditis, which left him with



FIG. 4.—The patient is standing erect, and was told to activate both quadriceps muscles. The eminences at the middle of both thighs mark the locations of the proximal ends of the ruptured quadriceps muscles.

enlargement of the left and right ventricles. A loud blowing murmur could be heard during systole over the apex, which was interpreted as the result of an old mitral endocarditis.

These 2 cases bring out several characteristic features. In both instances there was disease of the body of the muscle, and in one case the disease was so extensive that a number of skeletal muscles were ruptured by slight violence (Fig. 4). In both instances the muscular disease accompanied an acute arthritis, and in the first case all pain was associated with passive stretching of the muscle, and not with activation. In both cases there was not only decided evidence of disease of the belly of the muscles, but there was a want of evidence of disease in the perimuscular structures.

Dermatomyositis.—In 1887 Unverricht¹ described a case which he named *perimyositis acuta*. The patient was a young man who had acute inflammation, edema, and tenderness of many skeletal muscles, viz., the extensors, the vasti of the thigh, and the muscles of the back and neck. The laryngeal and pharyngeal muscles, the diaphragm, and the eye-muscles were free. Unverricht emphasized this fact as evidence against the possibility that the case was one of trichinosis, and at the autopsy a careful search for trichinæ proved negative.

ETIOLOGY.—Unverricht says in the article mentioned above that we are coming to recognize that acute inflammation and degeneration of the muscles may occur without lesions of the anterior horns of the gray matter of the spinal cord, contrary to the view of Charcot, which had dominated the field up to that time. Unverricht believed that his case was one of rheumatic infection, and although he attached no importance to the fact, he stated that traction on the muscles caused pain, whereas the patient was able to walk with only moderate discomfort.

SYMPTOMATOLOGY.—In a later publication a case of dermatomyositis is described by Unverricht as beginning with fever, splenic swelling, edema, erythema of the skin, urticaria, and infiltrating nodules. Ultimately the muscles of swallowing may be involved, and also the intercostals, but the muscles of the eye, heart, tongue, and diaphragm escape. The patients ultimately succumb to suffocation, with pulmonary disease. Dermatomyositis is a good term, and there is no adequate reason for suspecting that disease of the peripheral nerves is the original lesion. The atrophic muscles do not show signs of the reaction of degeneration. The skin may show erythema or measles-like eruptions, which disappear, leaving only brown pigments behind. Hemorrhage into the skin and into the intestine have occurred in some cases, but can be explained only on the basis of a constitutional infection. Muscles have been found in all stages of degeneration. The fibrillæ have been seen to be differently involved. In some instances the entire length was swollen, with hyalin and fatty degeneration. There were also transverse lesions, as well as lesions involving the entire length.

The shortest duration of any reported case was eight days, and

four months is about the longest duration of any of the acute fatal cases. The pathologic picture of the disease is essentially a perimyositis and infiltration of the muscles with interstitial exudation. There is some question as to whether or not the massive disease of the muscles is not secondary to the intermuscular inflammation. A bacteriological solution of dermatomyositis is thus far wanting.

Clinical History.—Only 3 instances of dermatomyositis have come under the writer's observations. The first of these occurred in the case of a negro, twenty-six years of age. This man had noticed for nearly three years prior to his entrance to the hospital that his hands and feet were swollen when he rose in the morning, and about one year before entrance there was swelling, redness and tenderness of the ankles, knees, wrists, and shoulders, with fever. Nine months before entrance the patient noticed that his calves were becoming stiff and that the skin felt tough. During the previous year he had been considerably embarrassed by what he described as a hide-bound condition of his skin, which did not permit free movements in the ankles, forearms and shoulders, and also impaired the movements of the muscles of his face. The skin was smooth and glossy, and both skin and subcutaneous tissue were hard and tough. There was a lack of the normal oil of the skin, and no sweat. One could not pick up the skin in folds anywhere on the body except about the genitalia. There was no normal glide of the muscles under the skin; skin and muscle moved together. When one palpated over the tendon-sheaths and over the muscles during motion, a definite crepitation was felt, similar to the creaking of a Russia leather binding, and a grating was felt when the muscles were passively moved. There was no muscular atrophy or sign of any old arthritis. The patellar reflexes were normal in degree and promptness. The man was unable to move the upper arm above the horizontal position, owing to restraint of his latissimus dorsi and pectoralis major. The involvement of the masseter muscles could be plainly palpated. The mouth could be only partly opened on account of the impaired extensibility of the masseters. On attempting to elicit electrical reactions in the forearm and leg-muscles, it was found that there was no sign of reaction of degeneration.

This patient remained in the hospital for about eight weeks, and at the end of that time left in about the same condition in which he had entered. During the entire time there was no elevation in temperature nor acute involvement of any joints.

The second instance of dermatomyositis to come under the writer's observation was the case of a man, fifty years of age, who entered the City Hospital in Cleveland on account of exhaustion and very distressing paresthesia, which he referred to both legs and feet. The man had cardiac enlargement, with the apex in the sixth interspace one inch outside the nipple line. There were no evidences of any valvular disease or of any disease of the aorta or peripheral vessels. The arterial pressure was 135/90. There was very moderate edema of the back of the neck and of the skin of the entire trunk and thighs. The edema

was due to an acute nephritis. The urine contained an abundance of albumin, hyaline and granular casts, leukocytes, and a few red-cells. There were very marked evidences of dermatomyositis in both legs and feet and in the vicinity of the neck and shoulders. The skin from the knees down to the toes had about a normal thickness but was of a parchment-like consistency, with intense bronzing over the affected area. The skin could not be wrinkled into folds, and was attached to the underlying tissues. There was no crepitation, for the fixation seemed too firm to admit of sufficient gliding of the skin to cause crepitation. The muscles of the calf of the leg were much diminished in size, and greatly increased in consistency, and so inelastic that dorsal flexion of the tarsus was prevented. When the patient stood upright, he could not raise the ends of the metatarsals from the floor. He could raise himself on his toes about half the normal distance. Passive plantar and dorsal flexion of the tarsus was very much hindered by the inelasticity of the muscles and of the underlying skin and fascia. The muscles were not sensitive to pressure, nor were they sensitive to traction or activation.

The patient was a Slav, with whom the author had great difficulty in communicating, but so far as could be learned from the man, there were no abnormal responses to any kind of test for the sensory percepts. All the arteries in the feet and legs were normal, and it seemed that the paresthesias from which he suffered could be traced to involvement of the peripheral nerves secondary to fibrosis of the skin and fascia. On the back of the neck the skin was thicker than normal, markedly indurated and deeply bronzed. Activation, traction, and pressure caused no pain so far as the muscles of the neck were concerned, but there was marked limitation in the anteroposterior and lateral flexion of the head on the trunk. The limitation in the neck muscles was due to the same process that limited the movement in the muscles of the leg and feet.

How long the dermatomyositis had existed in this man, it was impossible to learn. He seemed to have given little attention to it. The only thing that disturbed him was the paresthesia in his feet and legs, and he was led to seek relief at the hospital on account of progressive weakness attending his myocardial lesion, and nephritis. The author could find no evidences to explain the etiology of the process, but it seems to have been a case of dermatomyositis which was limited in extent and had reached a permanent stage. The only symptom of which the patient complained was the paresthesia, which seems to have been evidence of a secondary involvement of the peripheral nerves.

The third patient with dermatomyositis was a boy seventeen years old, who entered Lakeside Hospital in August, 1920. This patient had very extensive induration of nearly all the muscles of the face, neck, trunk, and extremities. The volume of the muscles in this instance seemed to be very well preserved. They were not painful, but they were indurated and had lost their normal capacity for extension, so

that the rigidity of the muscles was responsible for the limitations of movement. The dermatitis was very much less in extent than in the two preceding cases. The skin was thin, had a parchment-like texture, and was intensely bronzed, but there was not the same fixation of the skin to the underlying muscles as was described in the preceding cases.



FIG. 5.—The patient is trying to flex the head on the trunk, to throw the arms in the horizontal position, to bend the trunk on the thighs, and also to bend his knees.

The patient was not hide-bound, but he was muscle-bound. Besides these changes in the muscles and skin, there was some evidence of tenosynovitis located over the dorsal aspect of the wrists in the long extensor tendons of the fingers. The only clear evidences of a former arthritis were in the wrist joints. X-ray examinations were made of the bones and the note made that they were "thin and fragile."

540 INFLAMMATORY DISEASE OF SKELETAL MUSCLES

Of the two accompanying photographs, Fig. 5 shows the patient when directed to bend his head downward. He was also to throw his arms into as nearly the horizontal position as possible, and he is trying to bend the trunk on his thighs and to bend his knees, with the clearly depicted results. In photograph Fig. 6, the patient was instructed to straighten his arms at the elbow, to elevate them as high as he could,



FIG. 6.—The patient is trying to bend the head backward, to throw the arms upward, and to bend the trunk backward on the hips.

and also to bend backward and throw his head backward. The results of this effort, as shown in the photograph, very clearly depict the rigidity of all the muscles of the arm and thoraco-scapular and humeral muscles, also the rigidity of the anterior flexors of the head, and of the recti abdominalis and the flexor iliofemoral muscles.

The literature on the histology of myositis is all very much the same, and gives rise to the suspicion that one of the basic difficulties lies

in the fact that the histology of the normal muscle, in its relation to postmortem time, and method of hardening and of staining, has not been satisfactorily worked out. Saltykow² injected calomel, turpentine, and pyocyaneus emulsion into the femoral artery of rabbits and the same dose into the muscle. He used calomel, from 0.1 to 0.5 gram (1.543 to 7.716 grains) in 10 c.c. (2.71 fluidrams) of water; turpentine 0.5 to 1.5 gram (7.716 to 23.146 grains) in 10 c.c. of water in emulsion; pyocyaneus 1.0 to 3.0 c.c. (16 to 48.6 minims) of thin emulsion. The muscles were examined at varying periods after the treatment—three, seven and twenty-four hours. Saltykow found that the gross appearance of the muscles varied with the amount of the agent used. The muscle might be pale, or look much like the spleen, depending upon the amount of the agent employed. Within a few hours the muscle became stiff and inelastic. There was proliferation of the muscle-nuclei, as found in muscle changes of all kinds, in atrophy after section of the nerve supply, and in all other changes of pathologic origin. The disappearance of contractile substance was noted, and the presence of empty sarcolemma sheaths, infiltration of large and small lymphocytes, hyaline, granular and vacuolar degeneration of fibers. There were red areas from hemorrhage and white areas from cellular infiltration. In other words, there was nothing characteristic in the muscle changes to betray the etiology. It is only the severity of the process and the chronicity which determine the muscle changes in most of the processes. We find no explanation for the etiology of the disease in most of the cases of acute myositis.

A review of the reported cases of myositis associated with rheumatism shows very essential differences in the gross lesions in the course of the infection, and in the end-results. The rheumatic cases are not accompanied by acute or chronic skin manifestations like those found in dermatomyositis, and the rheumatic cases are not accompanied by perimyositis. The rheumatic cases of myositis which the writer has seen showed only intramuscular lesions, which involved single muscles and groups of muscles. The first case described is a very good instance of how extensive rheumatic myositis may be, and still confine itself within the sheath of a muscle. In this case there was an inflammation of the entire adductor magnus, and, in spite of its large extent, the single large muscle could be very clearly differentiated from all of its neighboring muscles. The rheumatic cases strongly suggest intramuscular metastatic infections; whereas dermatomyositis gives the symptoms of perimyositis with subsequent invasion of the intramuscular structures. A nervous factor has been introduced into the nomenclature with dermatomyositis on inadequate evidence. Peripheral nerve lesions were found in affected areas, but this involvement of the peripheral nerve was secondary to local inflammation and did not share in the etiology of the disease.

TREATMENT.—There is no treatment of dermatomyositis which is of value in either the acute or the chronic stage. Until some further

progress is made in our knowledge of the infection and immunity to the disease, we cannot reasonably expect successful specific therapy in the acute or chronic stages of dermatomyositis. **Baths and fomentations, and massage** will no doubt ameliorate the symptoms and probably modify the stiffness which is so annoying to the patient. **Thiosinamin** might be used in the chronic stage, but the author has observed no success attending its employment. There is **little** to be expected from **salicylates**, which are so effective when used in sufficient doses for the treatment of acute multiple arthritis. In the author's own experience the salicylates have had no effect upon the duration or severity of the muscular lesions. We cannot look upon this therapeutic failure as evidence against the theory that myositis has etiological factors in common with synovitis. Although salicylates are very effective in acute rheumatic synovitis, they fail to affect endocarditis, endophlebitis, inflammations of the serous membrane, and chorea, all of which frequently occur coincidentally with acute rheumatic arthritis; and it is quite usual to see the joint lesions promptly subside under the influence of salicylates, while the above-mentioned lesions remain refractory to this treatment.

PATHOLOGY.—The pathology of dermatomyositis is in a very vague state. There are pathological indications that a certain group within this disease composes a clinical entity with a common etiology. Whether the chronic cases such as the author described have the same etiology as the earlier cases reported by Unverricht, Wagner, and Hepp, is doubtful, although there is much uniformity in the sequence of events, in the skin and muscles in both the acute and fatal cases and the chronic cases which survive. That the disease is infectious seems very certain. Sick⁴ reported 4 instances occurring in the case of nurses in the psychiatric clinic at Tübingen. There is very little in Sick's article which is illuminating, so far as the character of the disease is concerned, but the article is important inasmuch as it shows that an epidemic of multiple myositis may occur. There is further evidence that dermatomyositis is caused by an organism which has a selective property for skeletal muscles. Martinotti⁴ describes the case of an old man who developed fever and sepsis, and died within a few days. An autopsy showed several abscesses, the size of millet seeds, in the kidneys. The organism was isolated, and when cultures of either 1 c.c. or 1/10 c.c. were injected into animals, the colonization was always found in the muscles of the abdomen, hind- and fore-legs. Abscesses were found in the muscles, but they were always small—the size of a millet seed; Martinotti calls the organism *Staphylococcus pyogenes aureus myositidis*. He reported the autopsies only to illustrate the selective property of this organism for the muscles.

Mayesima⁵ observed a case of polymyositis from which he recovered *Micrococcus albus liquefaciens*. He proved agglutination of the organism with the serum of the patient. Mayesima believed that this patient was infected through the tonsils, and calls attention to the fact that the disease is never associated with suppuration of the muscles.

Schmitz⁶ cultivated *Staphylococcus pyogenes aureus* from a patient with acute multiple myositis, and was able to reproduce myositis in guinea pigs. The heart, liver, lungs and spleen were normal in experimental animals, and Schmitz thinks that the organism has a preference for skeletal muscles. He endorses the work of Martinotti, and states that in his animals there were abscesses in the muscles, but that the abscesses were extremely small.

Herbert Fox's⁷ case was one of polymyositis from which he recovered a *Micrococcus pyogenes*. There were some cultural differences between this organism and *aureus* and *albus*. Fox suggests that the organism may be *Micrococcus pyogenes myositidis*. He found that in the fifth generation the organism was agglutinated by the patient's serum.

Gout.—The objective signs of intramuscular changes in gout are not as clearly defined as are the gross pathological lesions of the rheumatic myositis. Inflammations of tendon-sheaths, bursæ, fascia, and aponeuroses are not uncommon in gout. Subcutaneous nodules occur in gout, and are just as well-defined and painful as are those which are more commonly seen, viz., the rheumatic nodules. An instance of this was seen in the case of an elderly woman suffering from gout and diabetes. She complained bitterly of pain in the hands, which rendered them almost useless. The fingers could not be extended, nor could the hands be firmly closed on account of the severe pain. The hands were both held in a semifixed position on account of the pain which attended both flexion and extension of the fingers. Over the ends of the third metacarpal bone of each hand, between the skin and palmar fascia, a small nodule the size of a French pea could be palpated, which had a firm consistency and was slightly mobile on its fascia attachment. These nodules were exquisitely sensitive to pressure. Under a dietetic regimen (which followed the starvation treatment), with the use of **atophan**, the pain and the nodules subsided. That fascia and tendons may be the seat of gouty deposits has long been known, but there are no clear accounts of gouty deposits within the skeletal muscles. However, gouty patients suffer from muscular cramps and muscular pains which are attended by the appearance of sensitive pressure points, and the muscles are sensitive to stretching, quite like the muscles in rheumatic myositis. Inferentially, there seems excellent ground for suspecting the occurrence of intramuscular gout. This form of myositis is more amenable to treatment than is the rheumatic form. Patients with gouty manifestations in the bursæ, tendons and fascia respond quite well to treatment. The gouty dietetic regimen should be adopted, and **atophan** (tablets), grains $7\frac{1}{2}$ (0.492 gram), q.i.d., in half a glass of water after food, is very helpful. The atophan is best employed by using it three or four consecutive days in a week and then intermitting its use for the remainder of the week.

Myositis Fibrosa.—This very unusual disease is described by Batten.⁸ It begins as a subacute inflammation of the muscles, and produces a chronic myositis, which seeks successively various groups of muscles

and slowly advances. The lower extremities are usually attacked first, but cases are reported in which the inflammation started in the sternomastoid muscles and spread to the neck and back and intercostals, and later to the abdominal muscles. The case described by Batten was that of a child six years old. The disease began in the latter part of the first year of life. The condition progressed slowly. The child did not seem to have any pain, in which respect this case differed from other reported cases. Owing to the extremely hard and contracted abdominal muscles, the spine was fixed in a curved position and could not be straightened. The arms were fixed so that they could not be extended or adducted. He was rigidly fixed, and, in the flexed position, was unable to move or be moved except as a whole.

The writer has seen only one instance of myositis which could be termed myositis fibrosa. This patient was seen during a visit to the City Hospital in Cleveland. The patient was a young woman, twenty-five years old, who had suffered from her disease for nearly two years. She was greatly emaciated, and the ileofemoral and thigh muscles and the muscles of the shoulder-girdle were all involved, and, as in the case described by Batten, there was marked retraction of the recti abdominis. The muscles were very small, indurated, and sensitive to pressure. Any attempt to stretch them caused violent pain. The skeletal muscles were all transformed into small indurated bands. No joints were involved, and no other lesion in the body could be demonstrated beyond the extensive involvement of the muscles. The patient died shortly after admission to the hospital, and unfortunately autopsy was forbidden.

The etiological factor in this case remains unexplained, and so does its pathology. It was not even possible to offer any contribution to the gross pathology of the disease, but it seems worth while to mention the case because the disease strikingly conformed to the distribution and end-results of other cases of myositis fibrosa. The history and development of symptoms in this patient clearly indicated myositis, and the disease remained uncomplicated myositis up to the time of death.

Syphilitic Myositis.—Syphilitic myositis is a comparatively rare complaint, but it seems very probable that a syphilitic inflammatory process in the muscle may frequently occur without producing any symptoms of either a subjective or an objective character. A large proportion of the reported cases have shown the location to be in the ends of the muscle, near its junction with a tendon or aponeurosis. We may have a gummatous form, with necrosis and subsequent invasion of the skin, so that the disease will simulate a caseous tuberculous gland. The writer saw one such patient who had several sinuses about the lower end of the sternomastoid muscle. The lesion proved to be an ulcerating gumma from the lower end of the muscle, and promptly healed after **antisyphilitic treatment**. The sternocleidomastoid muscle, biceps, trapezius, masseter and temporal muscles have all been mentioned as favorite locations for syphilitic myositis. The locations have varied in the experiences of different writers, but the author's own experiences

have been confined to the sternocleidomastoid, the biceps, and the rectus abdominis. The rectus abdominis case was in a woman about thirty years of age, who discovered primary swellings in the upper extremity of the right rectus muscle. The mass was not sensitive to pressure, nor was it sensitive to activation of the muscle or to stretching. The entire mass promptly disappeared under antisyphilitic treatment, returned about a year later, and again disappeared under the same therapy.

Trichinosis.—In one instance of acute trichinosis, the patient, a young woman, entered the hospital with severe pain in the muscles of the upper and lower extremities. The patient was compelled to lie at rest in bed on account of the pain and the loss of muscular power. The muscles were sensitive to pressure and exquisitely so to stretching, but activation of the muscles was not painful. The patient could hold her leg extended on the thigh against strong resistance and suffer no pain, but if the knee was bent she complained of severe pain in the quadriceps muscle. The only diagnosis which could be made from the objective examination and the history was that of an acute multiple myositis. The blood-count showed no increase of eosinophils, but an excised fragment of the quadriceps muscle revealed an abundance of larvæ. This instance of trichinosis is mentioned because one may encounter instances where neither the history nor the clinical picture indicate anything beyond acute myositis. A widely-distributed acute myositis should always arouse a suspicion of trichinæ.

Gonorrheal Myositis.—This is a very rare complication of gonorrhea. The writer had one patient who developed a very painful supuration of the lower extremity of one of the peroneal muscles of the right side. The abscess was opened and gonococci were recovered from the pus.

No doubt of all the causes of acute muscular diseases, exposure to moisture and cold, gout, and rheumatism are the most frequent. Other infectious sources are rarely seen, but although they are rare, one must not neglect consideration of a muscle as the metastatic seat of any variety of infection.

Muscular Atrophy and Joint Diseases.—A never-failing but perplexing accompaniment of joint disease is an atrophy of the muscles on the proximal side of the joint. In the case of the knee-joint, the quadriceps muscle is invariably atrophied. When the hip-joint is involved, the gluteus maximus is atrophied. When the shoulder-joint is diseased, the deltoid muscle is always atrophied; other muscles may be involved, such as the supraspinatus and infraspinatus, and should the synarthrosis between the acromion process and the clavicle be involved, it is common for the cervical portions of the trapezius to be involved. The muscles of the arm are usually involved in diseases of the elbow, and atrophy of the forearm attends inflammation of the wrist-joint. When the carpal and phalangeal joints are involved, we see very marked atrophy of the interosseous thenar and hypothenar eminences. Deformity following

multiple arthritis may be due far more to muscular atrophy than to structural changes in the joint itself, and the protracted recovery of function after an attack of arthritis is largely due to muscular atrophy. Occasionally in multiple arthritis which has not lasted long and has left no deformity of the joint itself, the muscular atrophy may be so severe as to simulate primary muscular atrophy. Muscular atrophy is distinctly an attendant upon synovitis and does not result from peri-articular lesions. Patients may have peri-articular deposits about the knee-joint which occasion a great deal of disability and much pain, but if the synovial sac is not involved, there will be no atrophy of the quadriceps muscle; whereas a very moderate synovitis of the knee-joint, which may last only a few days, will cause a clearly demonstrable atrophy of this large muscle. The atrophy is not due to disuse, for the disuse may be quite as pronounced from any other source, but the promptness and the degree of atrophy are strikingly characteristic of all cases in which there is a lesion of the synovial sac. The tendon reflex of the muscles is always exalted; in fact, atrophy with exaggeration in tendon reflex is such a constant accompaniment of synovitis of any joint that, if the patient gives a history of recent inflammation of the knee-joint and there is no atrophy or exaggeration of the patellar reflex on the affected side, one is justified in assuming that there could have been no recent lesion of the knee-joint.

The pathological physiology of both the atrophy and the exaggeration of the reflexes is unexplained, and the author knows of only one point of view which throws any light upon the subject. Hoffa of Würzburg conceived the idea years ago that the atrophy was due to some afferent impulse along the nerve supply of the affected region. His first procedure was to cut all of the posterior nerve-roots of the sciatic nerve. He then injected bacterial cultures into the knee-joint in animals whose nerve supply was intact and also into the animals in which there had been a previous section of the posterior nerve-roots. Hoffa found that, when the posterior nerve-roots to the region were cut, the acute infectious synovitis was not attended by muscular atrophy; whereas it invariably occurred when synovitis was produced in animals with intact nerve supply. This of course does not amount to a solution of the problem, but it does offer considerable evidence that the atrophy and exaggeration of reflexes are due to some unknown modification of the lower neuron through the agency of the afferent paths of the peripheral nerve.

REFERENCES

1. Eulenburg. *Realencyklopädie des Gesammtheitskunde*, 4th Ed., 1887, xii, 1.
2. Saltykow. In *Virchow's Archiv*, 1903, clxxi, 118.
3. Sick. *Münch. med. Wehnschr.*, 1905, lii, 1092.
4. Martinotti. *Centralbl. f. Bakt. u. Parasitenk.*, 1898, 1ste Abt., xxiii, 877.
5. Mayesima. *Deutsch. Ztschr. f. Chir.*, 1910, civ, 321.

6. Schmitz. Centralbl. f. Bakt. u. Parasitenk., Original, 1912, 1ste Abt., lxxv, 259.
7. Fox, H. Am. Jour. Med. Sci., 1913, clxv, 879.
8. Batten. Tr. Clin. Soc., London, 1904, xxxvii, 12-40a.

SECTION VIII
DISEASES OF THE KIDNEY

CHAPTER I

DISEASES OF THE KIDNEY

BY J. B. McELROY, B.S., M.D.

- Congenital nephropathies, p. 550:—Ectopic kidney, p. 550—Congenital malformations, p. 551:—Congenital single kidney, p. 551; Congenital atrophic kidney, p. 553; Lobulated fetal kidney, p. 554; Fused kidneys, p. 554:—Horseshoe kidney, p. 554; Fused single kidney, p. 556—Variations in renal pelvis and ureters, p. 557.
- Movable kidney, p. 558:—Etiology, p. 559; Symptomatology, p. 559; Diagnosis, p. 563; Treatment, p. 565; Pathology, p. 566; Historical summary, p. 566.
- Uremia, p. 566; Definition, p. 566; Symptomatology, p. 566; Clinical varieties, p. 570; Treatment, p. 571:—Eclamptic equivalents, p. 572; Uremia with kidney insufficiency, p. 573.
- Nephropathies of circulatory origin, p. 575:—Chronic passive congestion of kidneys, p. 575:—Definition, p. 575; Etiology, p. 576; Symptomatology, p. 576; Treatment, p. 581; Pathology, p. 583.
- Focal atherosclerotic kidney, p. 584:—Symptomatology, p. 584; Treatment, p. 585; Pathology, p. 585.
- Nephropathies generally included under the genetic term Bright's disease, p. 585:—Introduction, p. 585—Nephrosis, p. 588:—Definition, p. 588; Etiology, p. 588; Symptomatology, p. 590; Diagnosis, p. 594; Complications, p. 594; Clinical varieties, p. 594; Treatment, p. 595; Prognosis, p. 597; Pathology, p. 597.
- Amyloid kidney, p. 599.
- Necrotizing nephrosis, p. 601:—Symptomatology, p. 601; Treatment, p. 603; Prognosis, p. 603; Pathology, p. 604.
- Glomerulonephritides, p. 604:—Etiology, p. 604—Diffuse glomerulonephritis, p. 608:—Acute diffuse glomerulonephritis, p. 609:—Symptomatology, p. 609; Complications and sequelæ, p. 613; Treatment, p. 613; Prognosis, p. 618; Pathology, p. 618—Chronic diffuse glomerulonephritis, p. 627:—Etiology, p. 627; Symptomatology, p. 627; Diagnosis, p. 629; Complications, sequelæ and associated conditions, p. 630; Treatment, p. 630; Pathology, p. 630:—End stage of chronic diffuse glomerulonephritis, p. 637:—Symptomatology, p. 637; Diagnostic features, p. 642; Treatment, p. 643; Prognosis, p. 644; Pathology, p. 645.
- Focal nephritides, p. 654:—Acute focal glomerulonephritis, p. 654:—Pathology, p. 655—Chronic focal glomerulonephritis, p. 656—Septic interstitial nephritis, p. 656:—Pathology, p. 656—Embolie focal nephritis, p. 656:—Pathology, p. 657.
- The scleroses, p. 657:—Introduction, p. 657—Benign hypertension, p. 658:—Etiology, p. 658; Symptomatology, p. 660; Diagnostic features, p. 665; Treatment, p. 666; Prognosis, p. 668; Pathology, p. 669—Malig-

nant hypertension, p. 676:—Etiology, p. 676; Symptomatology, p. 677; Diagnostic features, p. 680; Treatment, p. 680; Prognosis, p. 680; Pathology, p. 680.
Bibliography, p. 686.

CONGENITAL NEPHROPATHIES

Congenital nephropathies may be considered under the head of displacements and malformations. Congenitally displaced kidneys are fixed and may or may not be deformed. Displacements with malformations will receive attention with the malformations. Of the congenital displacements of the kidneys, the most important is the ectopic kidney.

Ectopic Kidney.—Synonyms are pelvic kidney and dystopic kidney. The ectopic kidney is fixed in the bony pelvis or at the sacral promontory across the spine, and receives its blood supply from adjoining blood-vessels, such as the iliaes.

Braasch found 3 cases of ectopic kidney among 36 anomalous kidneys. Kelly and Burnam have had 8 cases. The right kidney is more frequently fixed in abnormal position than the left. The condition is due to the arrest of the kidney in its ascent during fetal development. If this takes place during the period from the second to the fifth week, it will be fixed in the pelvis; if later, it will be found above.

There may be no symptoms present, or symptoms due to pressure of the displaced kidney may be complained of, such as pains referred to the back and lower abdomen and intestinal disturbances. Symptoms due to associated pathological lesions such as hydronephrosis and calculus may also be present. On palpation a tumor, which may be mistaken for diseased uterus or adnexa or for an appendiceal mass, will be detected.

Cystoscopic examination may show an anomalous ureteral opening. The ureteral catheter can be passed only a short distance, but if it has passed into the pelvis of the kidney, as indicated by the discharge of urine, the abnormal position of the kidney may be located. This will be accomplished better by pyelography which will also show any anomalies of the renopelvic outline which may be present.

The diagnosis of ectopic kidney is of importance to the surgeon and obstetrician as it is likely to be confused with certain surgical conditions and sometimes causes serious dystocia.

The detection of a retroperitoneal mass associated with large blood-vessels, by rectal or vaginal examination, might suggest the presence of an ectopic kidney if one kept this condition in mind as a diagnostic possibility. Its presence can be confirmed only by special examinations—ureteral catheterization and pyelography.

According to Braasch, the most frequent complication of ectopic kidney is hydronephrosis. Kelly and Burnam found calculus in one. Genital anomalies are frequently associated with pelvic kidney.

The kidney is usually in the pelvis or lying across the spine at the sacral promontory, though it has been found in other peculiar positions, as near the inguinal ring and in a congenital umbilical hernia. The

pelvis of the kidney lies in front and the kidney itself is flattened posteriorly with deep anterior grooves to fit its bed. The vessels are abnormal, usually arising from those nearest to it as the common iliac, external iliac, etc.

Congenital Malformations.—Congenital malformations of the kidney have to do with variations in the number, size and form of the kidneys, and with variations in the pelvis, ureters and renal blood-vessels. Congenital absence of both kidneys has been noted in monstrosities, but the condition is incompatible with postnatal life. True supernumerary kidneys require that more than two anlagen be present and that they remain separate throughout development and ascent. True supernumerary kidney is very rare and has no clinical importance.

Variations in form and size have to do with lobulated fetal kidneys, fused kidneys and congenital cystic kidneys. The latter will be considered under a separate heading.

CONGENITAL SINGLE KIDNEY.—Synonyms are solitary kidney, and asymmetrical kidney. This condition requires that there be a complete absence of the kidney on one side.

Anders in a careful review of the literature up to 1910 determined that the expectation of the congenital single kidney gives a ratio of 1 in 1817 autopsies and that there was a total number of 286 cases. Of Kuster's cases 10 per cent. were in new-born babies. Of 154 cases collected by Anders, 34 were under ten years of age, which includes 13 premature births; 62 were between ten and fifty years of age; and 50 were over fifty years of age. Of 248 cases collected by Anders, 159 were males and 89 were females.

Agensis takes place early in fetal development from the third to fourth week. The anlage fails to develop from the wolffian duct which may itself be insufficiently developed; or the anlage may pass through the first stage, but becomes arrested or absorbed before it has completed its ascent.

The subjective symptoms are of little value, and when present are due to associated pathological lesions. On palpation the remaining kidney may be found enlarged. This will, however, only be suggestive since one of two kidneys may be found enlarged and lying low, and a tumor of surrounding organs may simulate an enlarged kidney. Cystoscopy will usually reveal only one ureteral orifice. Caution must be exercised in deciding upon the absence of one ureteral orifice, especially in an inflamed, contracted bladder. The injection of indigocarmin will here be of great assistance. If only one ureteral orifice is present, close inspection may reveal hypertrophy of the muscular ring about the ureteral orifice and the urine escaping more frequently and in greater volume than normally. Several cases have shown the presence of a portion of the ureter of the absent kidney. Under this condition two ureteral orifices will be present. The ureteral catheter can be passed only a short distance, and no urine will be seen coming from this side. Pyelography will show the pelvis of the kidney enlarged and normal in outline.

The diagnosis of congenital single kidney is of extreme importance to the surgeon, for in contemplated operations on this organ it is necessary to know whether both kidneys are present. Ransahoff has collected the records of eleven operations on solitary kidneys; of these four were nephrotomies and seven nephrectomies. The nephrectomies were fatal in from one to eleven days. The condition is perhaps of no less importance to the internist in view of the alarming symptoms which develop in case the remaining kidney becomes diseased, which is a result not unusual. The diagnosis must be made by special examination—cystoscopy, ureteral catheterization and pyelography, the results of which have been described above. Sometimes one kidney has been destroyed by pathological processes and it will be necessary to differentiate between this condition and congenital single kidney. In the acquired single kidney the signs of inflammation around the ureteral orifice are present, the ureteral orifices are usually in normal position, and as a rule the pelvis is not enlarged (Braasch). Functional kidney tests may be of corroborative value in the diagnosis of congenital single kidney, as the output of phenolsulphonephthalein from the compensatorily hypertrophied kidney may approximate the normal.

Complications are frequent in the congenital single kidney. Of 170 cases collected in 1910 by Anders, 79 showed morbid changes other than compensatory hypertrophy. These were as follows: chronic interstitial nephritis, 19; chronic nephritis (variety not specified), 11; chronic parenchymatous nephritis, 2; ureteral calculi, 9; pelvic calculi, 6; hydronephrosis, 4; pyelonephritis, 10; cystic kidney, 3; tuberculosis, 2; "diseased" kidney, 3; stone in the bladder, 1; carcinoma of the kidney, 1; cloudy swelling, 1; congested kidney, 1; amyloid kidney, 1; fatty kidney, 1; abscess of the kidney, 1. Of Braasch's (1912) 6 cases, there was tuberculosis in one and a kinked ureter producing partial obstruction in one. Of 3 cases of Kelly and Burnam (1914), there was stone and tuberculosis in one, stone and hydronephrosis in one, and tuberculosis in one.

Congenital single kidney is frequently associated with genital hypoplasia and sometimes with the absence of the adrenal gland on the affected side. Of 255 cases collected by Radasch (1908), 100 showed defective genitals. In 90 of these the lesion is specified. Forty-nine were in males as follows: absence of vas deferens, 22; absence of seminal vesicles, 20; absence of ejaculatory ducts, 9; absence of testicles, 15. Forty-one were in females as follows: uterus entirely absent or bicornate, 12; vagina absent or reduced by one-half, 5; oviducts absent, 9; ovaries absent, 4. In 151 cases collected by Anders, the suprarenal gland was absent on the affected side in 27.8 per cent.

There is always compensatory hypertrophy in the congenital single kidney. It is claimed that this is due to hyperplasia of the glomeruli and tubules brought about during fetal development, rather than to enlargement of individual glomeruli and tubules. During the ascent the kidney may cross the middle line and lodge in the lumbar region of the opposite side. There is usually an abnormal number of blood-

vessels—3 to 5 arteries and 3 to 4 veins arising from the large abdominal trunks. An unusual number of vascular twigs supplying fat or connective tissue are said to indicate the presence of a rudimentary kidney; and a number of large obliterated vessels are likewise said to indicate that the kidney had existed and had been destroyed by a pathological process. Of 153 cases in which the kidney and ureter were absent, L. Polack, in 1905, found that 89 were on the left side, 56 were on the right side and on the side not mentioned in 8. Of 286 collected by Anders in 1910, 153 were on the left side, 120 on the right, and on the side not stated in 13.

CONGENITAL ATROPHIC KIDNEY.—Synonyms are rudimentary kidney, fetal kidney, infantile kidney, and renal hypogenesis. There are two groups of these kidneys: in one there is development from only a portion of the renal anlage; in the other the kidney shows the usual form and construction, but is greatly reduced in size.

Morris places the frequency of the congenital atrophic kidney as .02 per cent. of all autopsies; Braasch saw 6 cases in 36 anomalies and Polack found 16 cases in 264 anomalies. The age at which death occurs varies. Of 66 cases collected by Gastaldi, 32 were in males, 10 were in females, 18 not stated. Of 9 cases of Coplin, 5 were in males and 4 were in females. Arrest in the embryonic development occurs from the seventh to the ninth week. Coplin emphasizes the relation of the condition to defective arteriogenesis.

There may be no symptoms at all, but several observers have attempted to construct a clinical syndrome characteristic of so-called hypogenetic nephritis. Besancon calls attention to chlorosis, headache, vomiting, lassitude, slight puffiness of the eyelids, slight diffuse edema of the lower extremities, frequent micturition and pale abundant urine. In a case studied by Stengel there was pregnancy associated with toxemia and eclampsia. The patient gave a history of kidney trouble all her life; the systolic blood-pressure was constantly above 200 mm.; there was a trace of albumin and a low specific gravity. The phthalein excretion was 40 per cent. in two hours and the non-protein nitrogen of the blood was from 33 to 36 mgs. (.5082 to .5564 grains) per 100 c.c. (3.38 fluid ounces).

With slight atrophy cystoscopic examination will show nothing abnormal. With marked atrophy it may show atrophy of the circular muscle about the meatus, slight meatal contraction and only an occasional and slight discharge of urine. The other meatus will show a compensatory increase. Due to the atrophy of the ureter which is usually present, it will be difficult to pass even a small catheter. Pyelography may show the pelvis so rudimentary as to corroborate the above findings.

In the diagnosis, nephritis, toxemia or uremia and especially cardiorenal disease in a young person are suggestive. The diagnosis can, however, be established only by the results of the special examinations mentioned above. Quantitative functional differences of both kidneys may be of corroborative value. Under certain pathological conditions atrophy of one kidney may be acquired. This may often be excluded

by the presence of genital hypoplasia which frequently accompanies the congenital atrophy.

The associated genital anomalies are usually on the same side as the renal defect, but Lombroso has reported a case in which it was on the opposite side. Renal dystopia and displacement of ovaries and testes may be present.

In those cases in which a portion of the renal anlage fails to develop, the pelvis and ureter may be represented by only a formless pouch at the end of a tube or a solid cord; or the cortex may develop but not to the extent of producing lobulation and subdivision of the medullary substance, when one or two pyramids instead of the usual number will be present. The anomaly is usually confined to one kidney, the other showing compensatory hypertrophy. The weight of the affected kidney may vary from one gram (15.43 grains) to normal. In 5 of Coplin's cases, the smaller averaged 75.8 grams (1169.594 grains) in weight and the larger 140.4 grams (2165.372 grains). Macroscopically the arteries are smaller than normal and have a small lumen in proportion to the thickness of their walls. Microscopically, evidence of arterial hypoplasia is seen in fragments of the external elastic membranes in the perivascular tissue, in its uneven thickness and diffuse waviness, and in the abnormal thickness of the muscular coat which contains more fibrous than muscular tissue. Further it is seen in the long irregular sweeps of this internal elastic membrane, and in its irregularity, imperfection and fragmentation. Superimposed upon these signs of defective arteriogenesis are the lesions of arteriosclerosis and primary contracted kidney. Of 60 cases analyzed by Coplin, 32 involved the right kidney and 28 the left.

THE LOBULATED FETAL KIDNEY.—Lobulation of the kidney usually disappears after the fourth year of life. Its persistence longer indicates that the growth of the cortex has not been vigorous enough to obliterate the depressions, or that the cortical columns were of such depth that the usual postfetal cortical growth was insufficient to fill in the grooves.

Most lobulated kidneys have abnormal arterial circulation, while the veins are more apt to be regular. They are much more susceptible to disease than smooth kidneys, tuberculosis being relatively frequent.

FUSED KIDNEYS.—There are two varieties of fused kidneys, the horseshoe kidney and the fused single kidney of which there are several subvarieties.

The Horseshoe Kidney.—Synonyms are *ren arcuatus*, and *ren unguiformis*. While, as the name indicates, this kidney in shape resembles a horseshoe, some of them are irregular and resemble the letter L. They result from fusion of the embryonic anlagen before the ascent of the kidneys from the pelvis take place.

The combined statistics of Morris and Socin show that horseshoe kidney occurred in .02 per cent. of 1600 autopsies. Braasch saw 8 cases in 36 anomalies of the kidney. It is more frequent in women than in men. Fusion of the embryonic anlagen takes place before the ascent of the kidneys out of the pelvis, that is, before the seventh week.

There may be no symptoms at all. Rosving has described a rather characteristic clinical syndrome occurring without the presence of pathological lesions. There is pain referred to the abdomen, lumbar region and epigastrium; it radiates downward; it is aggravated by standing, continuous jarring and muscular exercise; it is mitigated by rest and relieved by prolonged rest. There is also throbbing and a sense of pressure in the abdomen, aggravated by bending forward. Symptoms due to associated pathological lesions are present. With hydronephrosis there is swelling in the region of the displaced kidney, limitation or retention of urine, sudden relief of pain with the passage of a large quantity of urine of a low specific gravity, and chronic dragging pains referred to the back and lower abdomen. With pyonephrosis there is steadily increasing pain, increased by pressure over the swelling, relieved by discharge of pus, and associated with febrile symptoms. With nephrolithiasis, there is pain, associated with hematuria and often pyuria, increased by manipulation and exercise, and relieved by rest. With tuberculosis, there is enlargement with tenderness in the lower abdomen; slight hematuria, pyuria and the presence of tubercle bacilli in the urine; pollakiuria and dysuria with irritation of the ureteral orifice and the escape of purulent urine on the affected side; and a febrile temperature and evidence of tuberculosis elsewhere.

With cystic tumors there will be a swelling in the lower part of the abdomen. The swelling does not fluctuate; it is rounded and nodulated on the surface, and its general contour may suggest the horseshoe shape; it is not painful on pressure.

The horseshoe kidney may be associated with thrombosis of the iliac and femoral veins giving rise to edema of the legs and ascites. Upon palpation under an anesthetic, a mass might be felt and its contour made out in a thin individual as in a case of Newman. There was fusion of the upper pole of the kidney with the convexity upward.

The radiographic shadow is usually too inexact for satisfactory interpretation, though it is occasionally suggestive, especially when there is the shadow of a stone in the lower median abdomen. Meatoscopy may be of corroborative value. Obstruction of the ureteral catheters at a low level may suggest a renal anomaly. Pyelography will accurately determine the position of the pelvis as well as any deformity of the pelvis or ureters which may be present.

The diagnosis will be suggested by the clinical syndrome, by palpation, and the presence of genital defects which are frequently present, and definitely determined by the results of the special examinations, particularly pyelography.

Cryptorchidism, hypospadias, atresia of the veins, double or bicornate uterus, absence of the vagina and other genital defects have been found associated with horseshoe kidney. According to C. H. Mayo, the most frequent complication is hydronephrosis, which is more likely to occur in moderately young individuals. Pyonephrosis and lithiasis are seen less frequently and usually occur in middle age and later. Tuberculosis, sarcoma, and cystic tumors are also occasional complications.

In 90 per cent. of the cases fusion takes place at the lower poles of the kidney because they are closer together in the early stage of development. At the seventh week of fetal development, before which time the fusion usually takes place, the kidneys have not rotated; therefore the pelvis is usually found in front of the organ. The pelves do not fuse, because they are developed before parenchymatous fusion occurs. The ureters are frequently divided. The vessels are more numerous than usual, arise from the nearest arterial source and usually at a lower level than normal. They branch and enter the parenchyma mostly behind the pelvis. The kidneys as a rule do not rise higher than the level of the aortic bifurcation. The connecting bridge may be composed of only a fibrous band of tissue or more frequently of cortical tissue without medulla. The bridge is on a level with the aortic bifurcation, its anterior surface is lobulated with distinct depression in the center and its posterior surface is smooth. In about 10 per cent. of the cases fusion takes place at the upper poles of the kidney.

The Fused Single Kidney.—There are several varieties of this malformation, the unilateral elongated kidney (*ren elongatus*), the scutiform or shield-shaped kidney (*ren scutaneous*), and the lump kidney (*ren informis*). The symptoms are much like those of the congenital single kidney. Physical examination reveals a tumor which may simulate tumor or disease of the pelvic organs, such as ovarian or uterine tumors, hydrosalpinx, pyosalpinx, an appendiceal mass, tumors of intestinal, pancreatic or mesenteric origin, or bony tumors of the pelvis. Cystoscopy is usually of not much value as two normal ureteral orifices will be found in the normal position. Upon ureteral catheterization and injection of the pelvis, the condition will be suggested by the pain being referred to only one side. The renal pelvis may be accurately located by metal catheters or better by the injection of thorium and radiography.

Stein has called attention to the particular importance of the diagnosis to the surgeon to prevent catastrophies and unnecessary lumbar incisions and to the obstetrician, as this malformation may form even more serious obstacles in parturition than the pelvic kidney.

The presence of the tumor makes it necessary to differentiate the fused single kidney from cancer of the colon, hepatosis, nephroptosis and from a pathologically hypertrophied kidney and from a congenital single kidney. In cancer of the colon, the kidney mass is smooth and regular; there is no tympany above and below the kidney mass; cancer of the colon is usually associated with hemorrhage and intestinal obstruction; if there is no functional evidence of the latter, it may be determined by injection of bismuth and radiography. In hepatosis and nephroptosis, the liver and spleen are movable and can be raised to some degree; the fused single kidney is fixed in abnormal position. The pathologically hypertrophied kidney and the congenital single kidney can be differentiated and the diagnosis in all cases can be found only by special examination, especially pyelography.

Of 55 cases collected from the literature by Stein, the following

complications were shown: tuberculosis, 3; nephritis, 2; hydronephrosis, 1; hydronephrosis and nephrolithiasis, 1; pyonephrosis, 1; suppurative pyelonephritis, 1; nephrolithiasis, 1; hypertrophy of one kidney and atrophy of the other, 1.

Associated genital malformations are not so frequent as in pelvic kidney, but they occasionally occur. In the unilateral elongated kidney, both renal anlagen fuse and ascend together into one lumbar pocket. There are two varieties of the unilateral elongated kidney. They follow:

(1) The simple elongated kidney (*ren elongatus simplex*). In this variety, one kidney is on top of the other, the hilum is turned toward the vertebral column, the arteries arise separately from the aorta, the ureters and pelves are separate, and represent the persistence of the six weeks' stage of embryonic development.

(2) The sigmoid kidney (*ren sigmoidus*). In this variety, one kidney is above with the hilum in the usual position; the other is below with the hilum facing in an opposite direction; there is a groove where the kidneys fuse; the ureters may cross; the arteries are separate, abnormal in origin and there is sometimes an accessory artery. In the scutiform or shield-shaped kidney, fusion takes place early—four to six weeks—and is complete; the position is low in the median line of the body, usually in the hollow of the sacrum; there are usually two arteries, rarely one; there are two varieties, the round and the flat.

The lump kidney (*ren informis*) is an irregular shaped mass composed of lobes of different sizes. Its position is just above the sacral promontory. There are from one to four short ureters in the anterior surface. The vessels enter the parenchyma in the depressions between the lobules in various positions.

The fused single kidneys occur about one time in 8,178 autopsies. Stein in 1916 collected 57 cases from the literature. It is about twice as frequent in men as in women, which is in contrast with reference to the occurrence of horseshoe kidney in the two sexes.

VARIATIONS IN RENAL PELVIS AND URETERS.—Of the variations in the renal pelves and ureters may be mentioned variations in the form and position of the pelves, duplication of the pelvis, cleft ureters, double and triple ureters, and anomalies of the lower end of the ureters.

Anomalies of the upper end such as obliquity of insertion of ureter into pelvis, absence of pelvis, and half a pelvis may give rise to symptoms of hydronephrosis. Abnormal openings of the lower end of the ureter in the male may also give rise to symptoms of ureteral dilatation and hydronephrosis. Incontinence and constant dribbling of urine which is a frequent and very annoying symptom in the female is not present in the male, since the abnormal opening is never anterior to the compressor urethræ in the male.

The diagnosis is established by cystoscopy, ureteral catheterization by metal catheters, and pyelography. Precocious splitting of the ureter, cleft ureter, is due to the nondevelopment of the primitive renal pelvis, the pole tubules developing precociously and then ascending parallel to each other. The cleavage may extend downward into the undivided

portion of the ureter so that finally the latter is cleft right to its entrance into the bladder. Double and triple ureters are of a regressive nature. They arise as two or three ureteric buds from the primitive excretory ducts. These multiple ureteric buds do not develop equally, the most caudal one showing the strongest development, not only as regards the expansion of its ureteric tree, but also as regards the height that it reaches in development (Felix). The ureter will open into the rectum if the wolffian duct and ureter fail to shift anteriorly from the cloaca before the urorectal septum grows down to divide the rectum from the bladder. If the ureter does not separate from the wolffian duct as usual, it may open into the organs developed from the wolffian duct—in the male, vas deferens, seminal vesicles, ejaculating duct; in the female, Gartner's duct.

It will be attached to the uterus and vagina if it does not remain isolated from the Müllerian duct. If the ureter is not detached from the wolffian duct after the sixth week of embryonic life it may be found opening into the urogenital sinus or the organs developing from this—the ureter in both sexes and the vestibule of the vagina in the female (Kelly and Burnam).

MOVABLE KIDNEY

(*Ren Mobilis, Wandering Kidney, Floating Kidney, Nephroptosis, and Dislocated Kidney.*)

Although Langdon formerly maintained that the normal kidney is absolutely fixed, it is now generally agreed that it has under normal conditions slight motility in three directions, longitudinal, anteroposteriorly and around the axis of its pedicle. The up-and-down movement with respiration and with body position is the greatest and varies within narrow limits, according to different authors. Thus, Piersol says that this movement does not much exceed 2 cm. (.8 in.); Harris says that it varies from 2 to 4 cm.; while Kelly and Burnam state that the longitudinal motility is from 2 to 5 cm. The other movements are very slight. English observers, especially, formerly applied the term "floating kidney" to such as had a mesonephron by which it hung out into the abdominal cavity. Now, any kidney which exceeds the normal motility is designated a movable kidney. With the patient in the dorsal position, the kidneys as a rule cannot be palpated. The right occasionally, and both in emaciated individuals may sometimes be felt. In the left lateral position, the right kidney may be palpated in most women, but not in men.

Various observers have arbitrarily classified the degrees of motility. Hilbert recognized two stages: first the palpable kidney, in which the lower pole or less than the lower half can be felt; second, the movable kidney, in which the whole kidney can be felt and isolated with the fingers. Glenard recognized four stages. The first corresponded to the first stages of Hilbert; in the second the whole kidney may be felt, but the fingers cannot be inserted above the upper pole; in the third, the

kidney may be "captured"; in the fourth, the kidney floats independently of respiratory motion. A useful classification is into three stages. The "palpable kidney," which may just be felt; the "movable kidney," which may be captured; and the "floating kidney," which may be moved to the brim of the pelvis or beyond the median line of the abdomen.

Etiology.—Movable kidney occurs quite frequently in women, being variously estimated from 4.41 to 56 per cent. of all women. It is much more frequent in women than in men, about 1 to 6, and is about 13 times more frequent on the right side than on the left. Considerations of the factors which hold the kidney in its normal position will explain the cause of its occurrence. These are: (1) Special body form; (2) the perirenal fascia in conjunction with the peritoneum; (3) the peritoneum, when this exists as a covering; (4) the renal vessels; (5) intra-abdominal pressure; and (6) the shape of the renal fossæ. There has been for a long time and still is considerable discussion as to which of these is the most important causative factor. Harris in a very careful and apparently convincing study arrived at the following conclusions: (1) The essential cause of movable kidney lies in a peculiar body form; (2) the chief characteristic of this body form is a marked contraction of the lower end of the middle zone of the body with a diminution of this portion of the body cavity; (3) this diminution in the capacity of the middle zone depresses the kidney so that the constricted outlet of the zone comes above the center of the organ and all acts such as coughing, straining, lifting, etc., which tend to adduct the lower ribs, press on the upper pole of the kidney and crowd it still further downward; (4) it is the long-continued repetition in suitable body form of these influences, which collectively may be called internal traumata that gradually produces a movable kidney; and (5) a distinctly movable kidney is never the immediate result of a single injury or external trauma. In this last proposition Harris is supported by Sulzer, Budinger and Gutterbach. Kelly and Burnam, while not attaching the same importance to peculiar body form as Harris, Becker and Leunoff, sum up a discussion of the etiology in these words, "Movable kidney then seems to depend upon a number of predisposing causes. The predisposing causes are especially body form and laxness of the supporting structures of the kidney. The actual causes are various acute and chronic traumata."

Symptomatology.—No symptoms at all occur in the majority of cases. Kelly estimates that only 1 in 10 are accompanied by symptoms; Brewer 1 in 11; while Curschman found symptoms in 68 of 270 cases. The severity of the symptoms is not proportional to the degree of displacement. Edebohls has observed that the severest pain is associated with movement of from 4 to 10 cm. (1.6 to 4 ins.).

PAIN.—There are two main conditions upon which pain in movable kidney depends, and accordingly as one or the other of these is operative we will have two groups of cases with reference to pain. The first group is due to traction upon and irritation of nerves by the displaced kidney. Actual pain is not a prominent feature of this group. The patient is

more likely to complain of an almost unendurable sense of weakness in the abdomen. There is rarely local pain in the kidney region. As the result of the irritation of the lumbar plexus, pain and discomfort may be complained of in the distribution of the branches of this plexus. Thus through the eleventh and twelfth dorsal, the ilio-inguinal, the iliohypogastric, the obturator, the crural and sciatic nerves, pain may be referred to the lower abdominal wall, the outer and inner side of the thigh, the genitals, the knee and the heel. Through traction on the diaphragm pain may be referred to the shoulder through the phrenic and supra-acromial nerves. According to Kelly, these referred pains are not of very frequent occurrence. Pains with the characteristics of biliary colic may be present, due to the pressure of the right kidney upon the common bile duct. True reflected pain is rarely present in this group. These pains are increased by the erect posture and exercise, in some cases by menstruation, upon removing the corset at night, by constipation, by pregnancy, although McAlister states that they sometimes disappear in pregnancy. Generally they are relieved or mitigated by rest, lying down.

In the second group pain is a more prominent feature and is due to kinking and twisting of the renal pedicle. If only the vein is obstructed the pain has the characteristics of that of passive hyperemia of the kidney and is due to the stretching of the kidney capsule. The pain in the lumbar region is dull, gradual and heavy, although, if the obstruction is sufficient to produce hematuria, the pains may resemble those of renal colic. If the ureter is obstructed, the pains are more severe and are due to the resulting hydronephrosis. Not infrequently the syndrome described by Dietl in 1864 is observed and is known as Dietl's crisis. The pain in the abdomen is severe, radiating to the lumbar region and along the course of the ureter. They are accompanied by nausea and vomiting and sometimes by symptoms of collapse. Not infrequently there is a rise in temperature, and palpation will elicit tenderness over the kidney and in the abdomen. Swelling of the kidney is rarely so great as to be recognized by palpation. During the attack, there is usually oliguria and sometimes a reflex anuria is present. The attack lasts from 6 to 48 hours and is followed by a transient polyuria. The attack may occur immediately after the obstruction or only when the hydronephrosis has reached a certain degree. They usually come on after excessive or violent motion.

In this group, contrary to the other, true reflected pain is met with. These may be complained of in the kidney zone of the affected or the opposite side. The disturbance in the kidney is transmitted through the sympathetic to the tenth, eleventh and twelfth dorsal and first lumbar segments of the cord and the pains are complained of in the distribution of the cerebrospinal nerves arising from these segments on the same or opposite side.

Pain in movable kidney may also result from associated conditions such as calculus, pyelitis, tuberculosis and inflammation of the kidney.

GASTRO-INTESTINAL SYMPTOMS.—Symptoms on the part of the stomach are quite frequent, especially the symptoms of so-called nervous dyspep-

sia, gastric pain, anorexia, nausea and vomiting. These symptoms are frequently attributed to nervous origin, but Kelly is inclined to refer them to the mechanical action of the displaced right kidney on the stomach for the following reasons: first, they occur most frequently with movable right kidney; second, suspension of the right kidney usually relieves the symptoms; third, suspension of the left kidney does not.

Frequently these symptoms are due to the associated splachnoptosis. Owing to the lack of mesentery in the second portion of the duodenum it is prevented from moving downward when it is dragged upon through its areolar tissue connection with the displaced right kidney and consequently it is stretched so that its lumen is diminished, giving rise to symptoms of the secondarily dilated stomach. These may be the symptoms of acute or chronic dilatation.

According to Bryan, the dislocated right kidney increases the dependent loop formed by the junction of the ascending and transverse colon, producing engorgement of the caput coli with the following resulting symptoms: pain, discomfort and heaviness in this region; a boggy tumor; febrile reaction; flatulence; and chronic constipation alternating with acute diarrhea. If the dislocated kidney constricts the superior mesenteric artery the symptoms of mucous colitis may be present. Symptoms of intestinal obstruction have been observed as a result of pressure of the displaced kidney on the intestinal tract. According to Edebohls symptoms of appendicitis are frequently associated with movable kidney and he thinks that they are due to the pressure of the kidney on the superior mesenteric vein, thus interfering with the return flow of blood from the appendix.

GALL-BLADDER SYMPTOMS.—As a result of the traction and pressure upon the common bile duct by the movable kidney, the passage of bile is interfered with, giving rise to typical attacks of biliary colic. There is the severe pain, with its more or less characteristic distribution, associated with nausea and vomiting and sometimes with a transient jaundice. However, these symptoms in movable kidney are rare and, according to Kelly, injection of the renal pelvis with sterile solutions does not reproduce the pain.

GENITO-URINARY SYMPTOMS.—Symptoms of pelvic congestion, as leukorrhea, dysmenorrhea, and intermenstrual pain are often observed in movable kidney. As Goelet has observed these symptoms in 75 per cent. of cases, he is inclined to refer the pelvic congestion to the displaced kidney. Schede reports a case in which both ovaries and uterus were removed without relief of the symptoms, which were subsequently relieved by anchoring the kidney. According to Kelly, the symptoms, except dysmenorrhea, are rare and are to be attributed to associated disturbance of the pelvic organs such as retroflexion of the uterus.

Pollakiuria is frequent during attacks of Dietl's crisis, but other manifestations on the part of the bladder are due to other causes than those dependent upon movable kidney. The urinary findings are normal in uncomplicated movable kidney. Oliguria followed by polyuria is

frequently observed as the result of transient hydronephrosis produced by obstruction of the ureter by the displaced kidney. When the vein alone is obstructed, oliguria may result from passive hyperemia of the kidney. Hematuria may result from interference of the return flow of blood by obstruction of the renal vessels and ureter. The hematuria may be slight or marked, intermittent or long-continued. It is, however, not sufficient to give rise to the signs of a severe secondary anemia. Kelly would seem inclined to discredit macroscopical hematuria to movable kidney and if no other cause can be discovered to refer it to the essential hematurias. The following case of long-continued intermittent hematuria seen in consultation with Dr. George Livermore, who furnished the main data obtained in the case would seem to the author to be due to a movable kidney. The patient was a young married woman, nullipara. The symptoms in the main were pains in the right side and lower abdomen, no distinct colic and general nervousness, associated with several attacks of intermittent hematuria, the last attack having continued for several weeks. Physical examination showed the young woman with nutrition below par and a movable right kidney of the first degree. The blood did not show a very marked degree of anemia, Hgb. 70 per cent. There was no leukocytosis. X-ray examination was negative for calculus. Cystoscopic examination revealed normal bladder and ureteral orifices. Ureteral catheterization with the subcutaneous injection of indigocarmine showed the time of appearance of the dye about the same on both sides. The urine from the left kidney was clear, contained no albumin, no blood and no casts. That from the right kidney was bloody, contained albumin, red blood-cells and casts. Careful examination of same did not show tubercle bacilli and animal injection of same gave negative results. Under absolute rest in bed and stypticin all symptoms, including the hematuria, promptly disappeared.

Albuminuria alone or accompanied with cylindruria occurs in movable kidney associated with obstruction of the vein or of the renal vessels and ureter, and disappears with the relief of the obstruction.

Reports of the results of modern tests for renal function in the movable kidney are meager. In uncomplicated cases there is usually no difference in the time of appearance of injected dye on the two sides.

NERVOUS SYMPTOMS.—In the absence of local symptoms referable to the displaced kidney, nervous symptoms are usually absent. With these, however, they are quite frequent. They consist of general nervousness and of the symptoms of neurasthenia and hysteria. They are due to nerve irritation and the mental disturbance as a result of the knowledge of the presence of a movable kidney.

REFLEX FUNCTIONAL SYMPTOMS.—Symptoms on the part of the circulation, respiration and sensation may be met with as the result of reflex functional disturbance.

PHYSICAL EXAMINATION.—Inspection in these cases will usually show a condition of nutrition below par. This is not the result of the kidney condition, but rather one of the predisposing causes frequently present.

Not infrequently will movable kidney be present in well-nourished patients. Mensuration will show a peculiar body form in these cases, which is also a predisposing cause rather than the effect of the movable kidney. According to Harris, the body cavity is divided into three zones; the upper being limited below by a horizontal plane at the level of the lower end of the sternum; the middle by one at the level of the tenth rib; and the lower zone, embracing all of the body cavity below this latter boundary. A diminution in the capacity of the middle zone will be found in all cases. The capacity of this zone is best estimated, according to Harris, by dividing the middle lateral diameter by the upper lateral diameter and multiplying the result by 100. The middle lateral diameter is obtained by measuring with calibrated callipers the greatest distance between the lower borders of the tenth ribs on both sides; the upper lateral diameter by determining by the same method the greatest distance between the lower borders of the seventh ribs. The normal index is 81.8 cm. Values for the index above this figure indicate the diminution in the capacity of the middle zone and will be found in all cases of movable kidney.

Palpation will in the greatest number of cases reveal the presence of a movable kidney. There are three methods in use in performing palpation. The dorsal method was first popularized by Frank. The patient lies on the back with the knees drawn up and thigh flexed on the abdomen to relax the muscles of the abdominal wall. The examiner stands at the side of the kidney to be examined, with the left hand in the flank and the right hand on the abdominal wall over the kidney. The patient is requested to breathe deeply and the kidney is felt best by the posterior hand as it descends and ascends with inspiration and expiration. The lateral position is known as Israel's method. To examine the right kidney the patient is in Sim's position, the examiner is on either side of the patient with one hand in front and the other in the back. The patient breathes deeply and the kidney is best palpated by the hand in front. To examine the left kidney the positions are reversed. The examination by this method will be positive more frequently than by the dorsal method. A third method is the use of the erect position. The patient places the foot on the side to be examined on a stool and bends the body slightly to the same side. This method will sometimes give positive results when the other methods fail. If the kidney is only slightly movable, a smooth rounded body will be felt. When quite movable the kidney can be grasped between the hands, and its outline be made out. Firm pressure will cause the patient to complain of a sickening sensation. In some cases the pulsation of the kidney vessels may be detected. The slipping back of the kidney with each expiration is quite characteristic. Percussion is practically of no value to determine the presence of a movable kidney.

Diagnosis.—There is no diagnostic syndrome of symptoms for nephroptosis. Examination by the x-ray may confirm the results of palpation and sometimes show abnormal motility where the latter method is negative. It will also accurately determine the degree of motility. The

pelvis of the kidney is injected with thorium X and one plate exposed with the patient in the prone position and a second one with the patient in the erect posture. The different positions of the kidney will be readily shown. With the presence of a movable kidney it becomes important to determine whether the symptoms presented by the patient should be referred to the kidney. For this purpose Kelly has suggested the injection of the pelvis of the kidney with colored sterile solution, being careful to use a large ureteral catheter to prevent back-flow. He states that this method will reproduce the pain complained of by the patient either in the presence or absence of a hydronephrosis.

Other conditions may produce symptoms similar to those produced by movable kidney and will have to be differentiated from it. Sciatica may have to be differentiated. In movable kidney the pain is not limited to the sciatic nerve; the anterior crural is often involved with it; the sciatic is not painful to pressure, is accompanied by a desire to urinate, and is not influenced by exposure to cold and dampness; there is no loss of motor power or atrophy of the muscles; it is increased by exercise and relieved by rest in bed, and is not prone to nocturnal exacerbations; there are digestive disturbances associated with exercise and jolting; there are intervals of complete rest and comfort; and there is temporary relief from medicinal measures for the digestive disturbances associated with absolute rest in bed.

The tumor presented by a movable kidney may have to be differentiated from hydrops of the gall-bladder; the kidney outline may be made out on palpation; there is no tenderness on pressure in movable kidney unless the kidney is diseased; movable kidney has a wider range of movement and when released has a tendency to return to the right lumbar region.

The pains of movable kidney may be differentiated from those due to chronic appendicitis by establishing the presence of abnormal motility by palpation or the x-ray, and the reproduction of the pain by injecting the pelvis of the kidney. Both conditions, however, frequently coexist.

Movable kidney is differentiated from tuberculosis of the kidney by the following findings in the latter: slight hematuria, pyuria, polyuria and the presence of tubercle bacilli in the urine; frequent painful urination, with irritation of the ureteral orifice on the affected side; the evidence of tuberculosis elsewhere.

It is differentiated from nephrolithiasis by the x-ray which will in the majority of cases show the stone, the ureteral orifice diseased and an increased number of urine shoots. In the movable kidney there is sudden diminution of urine, sometimes with the coincident appearance of hematuria and blood casts, and increased vascular tension with enlargement of the kidney.

Diseases of the stomach may have to be differentiated by careful special examination directed to this organ.

Among the complications of movable kidney may be mentioned hydronephrosis, passive hyperemia and atrophy of the kidney, adhesion

of the kidney to the anterior edge of the right lobe of the liver, hydrops of the gall-bladder and dilatation of the stomach.

It is frequently associated with other conditions, among which may be mentioned deformities of the liver, splanchnoptosis, hernia, misplacements of the uterus, appendicitis, nephrolithiasis, pyelitis, tuberculosis of the kidney and nephritis.

Treatment.—Patients possessing the peculiar body form of movable kidney should be advised as to certain prophylactic measures with respect to the avoidance or correction of certain conditions which are known to act as predisposing causes in the production of movable kidney. They should be advised to take **exercises calculated to strengthen the body wall**. They should be **advised against** wearing **tight bands** about the lower chest, and women especially **against tight lacing**. The body should be kept in a good state of nutrition by the proper attention to **diet, personal hygiene and exercise**. In these cases careful attention should be paid to care of these patients in labor and during the puerperium.

Possibly not more than 20 per cent. of these patients complain of symptoms, therefore the great majority of them present a condition to which the old saying "where ignorance is bliss, 'tis folly to be wise" is most appropriately applied. Unless the physician is quite sure that the symptoms complained of are due to the displaced kidney, he should exercise great care not to acquaint the patient with the knowledge of its existence. If a movable kidney with symptoms exists in a patient who is undernourished, measures directed to the improvement of nutrition should be carried out. (See treatment of Neurasthenia.) Symptomatic treatment is frequently necessary. The group with slight degrees of pain and digestive disturbances will usually be relieved by **rest in bed and mechanical support**. The severe pains of Dietl's crises will often require rest in bed and the hypodermatic administration of **morphin sulphate**, grain $\frac{1}{8}$ to $\frac{1}{2}$ (.008—.0324 gram); slight pains with hematuria, rest and **stypticin**, $\frac{1}{2}$ grain (.0324 gram) by mouth every 4 hours, continued for a day or two. Mechanical therapy by **belts or bandages** should be tried in every case of movable kidney. The results of this method of treatment are variable. It would seem to depend upon the kind of case and the observer, and unfortunately the kind of practice the latter is engaged in would seem to influence the result. Thus Morris, Edebohls and Harris regard it of little value, while Glénard thinks it is very effective; C. D. Aaron has reported 95 per cent. of cures in 414 cases and Sailer has never seen any good from surgical procedure. There are two principles to be observed in the application of the bandage. It should give support to the entire abdominal wall, bringing pressure to bear from below upward, and produce pressure immediately below the kidney to prevent its coming down. This can best be accomplished by the coöperation of the physician and the bandage maker. The bandage should be applied with the patient in the lying posture and worn continuously when she is moving about. The question of whether **surgical treatment** is necessary will often have to be considered by the general practitioner or internist. Each case

will have to be considered and the indications for operation are very fairly presented by Kelly and Burnam. In general, it would seem better to advise patients, who cannot afford the "rest cure" or who object seriously to wearing bandages, to be operated upon. This advice should also be given in cases in which a thorough trial of general measures combined with mechanical therapy fail, and the same in cases having frequent attacks of Dietl's crises. It is possibly better not to advise operation in cases associated with general visceroptosis. **Nephropexy** with the obliteration of the renal fossæ is generally regarded as the operation of choice.

Pathology.—The kidney is normal in the majority of cases. Fetal lobulation has frequently been noted. Hydronephrosis is frequently present and if it has existed a long time may lead to atrophy of the renal parenchyma. The right kidney has been found adherent to the liver. There is occasionally dilatation of the stomach and appendicitis is frequent. Deformities of the liver are often present, the result of tight lacing, and biliary stasis and hydrops of the gall-bladder may be present.

Historical Summary.—While movable kidney had been noted earlier by François Perdemontanous (1581), Riolan (1682), Pierre François Olive Rayer in his three-volume treatise on disease of the kidney, one of the epochal works in the history of these diseases, discussed movable kidney in all of its phases. The next notable contribution to the history of movable kidney was made by Dietl in 1864. Much discussion arose as to whether movable kidney existed independently of a general splanchnoptosis. Glénard maintained that it did not. In this view he was supported by Israel in Germany and Tuffier in Paris. The preponderating evidence, however, from kidney surgeons in America, England, France, and Germany is in favor of the opposite view. The first nephrectomy for movable kidney was performed by Gilmore, of Mobile, Ala., in 1870. This operation does not, however, now have the popularity of nephropexy which was introduced by Halen of Germany in 1881.

UREMIA

Definition.—The term uremia includes various symptom complexes presumably due to different causes such as toxemia and circulatory disturbances associated with diseases of the kidney and obstructive diseases of the urinary passages. It occurs most frequently in inflammatory conditions involving the kidneys, in bilateral surgical diseases of the kidney, and in conditions associated with anuria. It includes symptoms referable to the nervous, respiratory, circulatory, and digestive systems. All of these manifestations are very rarely present in any one case. The symptoms may occur at intervals or may be entirely latent.

Symptomatology.—**NERVOUS SYSTEM.**—*Convulsions* have been long regarded as among the most prominent manifestations of uremia. Pure eclamptic attacks are, however, relatively infrequent. Among 50 cases

occurring in the Memphis General Hospital and private practice in the last two years, there have been 8 cases. Of convulsive types of uremia, the eclamptic or epileptiform attacks are most frequent. They simulate very closely true epilepsy. Auræ may or may not be present. They may come on suddenly or be preceded by prodromal symptoms such as headache, drowsiness, stupor, dizziness, disturbances in the auditory and visual apparatuses or in the digestive system. The epileptic cry is usually absent. Tonic are succeeded by clonic convulsions. Usually there is sudden loss of consciousness during the attack, though it may be retained throughout. The convulsions are followed by a variable period of coma, or only a condition of somnolence may be present.

During the tonic stage, as a result of the involvement of the muscles of respiration, there may be marked cyanosis, turgidity of the veins, while during the succeeding clonic stage the tongue may be bitten. Not infrequently there is involuntary passage of the urine and feces. The respiration is embarrassed; the pulse, which before the attack is often tense and slow, during the attack is small, quickened, and often irregular, after the attack again becoming tense and slow. The blood-pressure is raised and, according to Ascoli, has a tendency to rise during the attack. Usually there is slight elevation of temperature. In this variety of uremia the pupils are most frequently dilated. The convulsive attacks may simulate jacksonian epilepsy, or the convulsions may be tetanic or choreiform in character, or the attack may set in with sudden coma without convulsions.

Instead of the eclamptic attacks various symptoms on the part of the nervous system occur which have been designated by some authors as *eclamptic equivalents*. Among these are *paralyses* of various kinds. There may be *hemiplegia* or *monoplegia*. The hemiplegia may be associated with aphasia or the latter may occur independently. *Amaurosis* is not rare; *hemianopsia* is less frequently present, and *color blindness* has been reported. Disturbances in the auditory apparatus occur. These may be of an irritative character such as ringing and buzzing noises in the ear; or of a paralytic nature, varying from difficulty in hearing to complete deafness. Increased reflexes, Babinski and Kernig's phenomena, and stiffness of the neck may be present singly or collectively. Among these may also be included headaches, frequently in form of migraine, dizziness, fainting attacks and various mental disturbances. The latter are variable; there may be only delirium associated with aphasia; or the patient may be irritable, restless or aggressive, or there may be depressive illusions or hallucinations which render the patient melancholic, and have been known to result in suicide. Certain characteristics help one to recognize these various symptoms or eclamptic equivalents as uremic. They occur quickly, run their course proportionately rapid; the paralytic phenomena may be associated with regional convulsions, which may occur first on one side of the body, then on the other; finally they all improve with improvement of the associated diseases.

Death may occur in the first eclamptic seizure, though it usually does not do so. The attacks show a great tendency to recur and frequently after repeated attacks death ensues. Although there are many theories as to the cause of the symptoms thus far described, it must be acknowledged that little is definitely known. Ascoli was able to produce convulsive seizures by the injection of nephrolysins into the subarachnoid space of certain animals and believed that such symptoms as above described were due to the nephrolysins arising from the destruction of kidney tissue in diseases of the kidney. The facts that eclamptic attacks were associated with increased cerebrospinal pressure and that the symptoms improve on lumbar puncture and limitation of salt and water and grow worse with a free salt and water intake, led Volhard and Fahr as well as other authors to refer the symptoms of the eclamptic attack to edema of the brain which is about the only lesion which can be demonstrated in this organ in cases coming to autopsy. Widal has referred the attacks to the impregnation of the cerebral and bulbar centers with sodium chlorid (chloruremia). Vaquez and others think they are due to a spasmodic contraction of the brain vessels as a result of the over-production of adrenalin. N. B. Foster has isolated a crystalline toxic substance from the blood of patients with eclamptic uremia. This substance was found to be rapidly fatal to guinea pigs and he thinks may be the cause of the convulsive attacks.

The eclamptic equivalents have been referred to vascular spasm on an arteriosclerotic basis (Forlanini, Pal, Vaquez, Osler). Here may be included also such symptoms as sensations of cold, paresthesia, dead fingers and toes due to vascular cramp as a result of arteriosclerosis of the arteries of the extremities and usually regarded as uremic. Still, most authors assume in addition the action of some toxic substance.

DIGESTIVE SYSTEM.—Scarcely less important than the symptoms referable to the nervous system are those due to disturbances in the alimentary tract. Among these are anorexia, nausea, vomiting, hiccup, stomatitis, and diarrhea. These may occur on a functional or an anatomical basis. Catarrhal and ulcerous stomatitis, hemorrhagic erosions of the stomach and intestinal ulcers have been described.

Inflammations of the serous membranes, pleurisy and pericarditis, and inflammations of the skin frequently occur as terminal events in kidney disease and have been regarded as manifestations of uremia. Ascoli's view that these conditions are to be considered uremic only in so far as the kidney disease and the uremia destroy the resistance of the tissues is now generally accepted. The same obscurity with respect to the real cause maintains here as in the other manifestations of uremia.

RESPIRATORY SYSTEM.—Dyspnea is a symptom which frequently occurs in renal disease and may be the result of different causes or conditions associated with the kidney disease, such as emphysema, bronchitis, cardiac failure, pulmonary edema, pneumonia, hydrothorax and hydropericardium. In contradistinction to the dyspnea arising from these causes, periodic asthmatic attacks associated with hypertension

and the periodic dyspnea of the Cheyne-Stokes' type are regarded as uremic. Hyperpnea may also be present and is referred to the acidosis which not infrequently is present in the uremic state.

SYMPTOMS DUE TO URINARY POISONING.—Besides these symptoms another group is present in uremia and has been referred to urinary poisoning by Ascoli and others. These include great mental and bodily weaknesses, apathy, stupor, inability to sleep soundly, labored and sighing respiration, dyspeptic symptoms, urinous odor of the breath, jerking of muscles and tendons, and fall of temperature; frequently they end in sudden cardiac failure.

FUNCTIONAL TESTS.—Functional kidney tests give very variable results in the different manifestations of uremia. In the eclamptic attacks associated with the acute and the second stage of diffuse glomerulonephritis, and in the eclamptic equivalents associated with hypertension of sclerotic conditions there is usually very little evidence of kidney insufficiency as indicated by the tests now used to determine the functional capacity of the kidneys. The non-protein nitrogen and urea in the blood are within normal limits; notwithstanding this, the urea index and Ambard's coefficient may show slight impaired functional capacity of the kidney.

Reiss states that there may be no evidence of salt retention even in exact metabolic studies of these cases, though the kidney test-meal may show low salt concentration and the phenolsulphonephthalein excretion in two hours may be slightly lowered. According to Reiss, there is no evidence of molecular concentration or increased osmotic tension in the blood. These statements may be illustrated in the following cases:

S., with a case of acute glomerulonephritis plus nephrosis, was attacked with convulsions followed by coma lasting forty-eight hours. The non-protein nitrogen of the blood showed 23.1 mg. per 100 c.c. blood.

G. M., with the second stage of glomerulonephritis, had convulsions, unconsciousness, delirium and great restlessness. The kidney test-meal showed a high fixed specific gravity of the day urine; a high specific gravity of the night urine; no night polyuria; a low salt concentration, day .093 per cent, night .55 per cent; a good nitrogen concentration, day 1.38 per cent., night 1.77 per cent.; and a phenolsulphonephthalein excretion of 45 per cent. in two hours.

In P., another case of chronic glomerulonephritis, with convulsions, coma, and dilated pupils, the kidney test-meal showed a good water excretion; a slight night polyuria, 624 c.c.; a low salt concentration, day .083 per cent., night .678 per cent.; a good nitrogen concentration, day .858 per cent., night 1.08 per cent.; and the non-protein nitrogen of the blood 28 mg. per 100 c.c.

B., probably with a case of benign hypertension with delirium, hallucinations and aphasia, showed a blood urea of .372 gram per liter; 12.61 grams of urea in twenty-four hours' urine; 6.6 grams of urea per liter of urine; a urea index of 32; an Ambard coefficient of .144; and a phenolsulphonephthalein excretion of 64 per cent. in two hours.

These cases are infrequent in comparison with those showing the symptoms of urinary poisoning, which according to some, especially Volhard and Fahr, deserve only the name uremia. In these there are marked evidences of serious impairment of kidney functions. There is marked retention of the Rest Nitrogen and urea, a low fixed specific gravity of the day urine, a low specific gravity of the night urine, low salt and nitrogen concentration, a low phenolsulphonephthalein excretion, a low urea index, a high Ambard coefficient, and increased osmotic tension of the blood. It must not be forgotten that convulsions, coma, and other cerebral symptoms may be combined with these cases. These functional tests may indicate impending uremia even in the absence of any symptoms of this condition, as in the following case which at the time of examination showed no symptoms at all indicative of uremia.

The functional tests showed a low fixed specific gravity of day urine; a night polyuria with low specific gravity; NaCl of day urine, .25 per cent., of night urine .3 per cent.; nitrogen of day urine .25 per cent., of night urine .288 per cent.; phenolsulphonephthalein 0 in two hours and a blood urea of 324 mg. per 100 c.c. Two weeks later the patient died with the mixed type of uremia, *i.e.*, symptoms of urinary poisoning and those of a psychotic nature and coma.

Clinical Varieties.—**TYPES OF UREMIA.**—Various classifications have been suggested for uremia. Rose Bradford and most authors of text books divide the manifestations of uremia into acute, chronic, fulminant, and latent forms. Ascoli, upon the basis of clinical observations, experimental results and theoretical considerations, recognizes two groups, *viz.*, renal uremia (*Nierensiechtum*) and urinary poisoning. The former includes increased blood-pressure, eclamptic attacks, stuporous and comatose conditions, mental disturbances, paralyses, disturbances of sensation, and amaurosis. In the latter Ascoli includes stupor, coma, a part of the mental disturbances, the weakened condition of the heart, the periodicity of the pulse and the breathing, the stomatitis and the conditions in general characteristic of chronic uremia.

Emil Reiss has classified uremia on a clinical basis into four forms:

(1) The asthenic form which is characterized by drowsiness and indifference, bodily fatigability, prostration, and sudden heart death. In the blood there is an increase of the non-protein nitrogen and osmotic tension.

(2) The convulsive or eclamptic form, characterized by the frequent occurrence of convulsive attacks which are extraordinarily similar to those of general epilepsy. Reiss also includes in this form paralyses. The external secretion of the kidney is perfectly intact.

(3) The psychotic form recognized by the predominance of psychical changes, at first marked confusion, hallucinations, illusions, later also deep coma, not only agonal. These conditions are mostly of a fleeting nature. There is in this form no retention of abnormal products of metabolism.

(4) The *mixed* form includes all of the symptoms occurring in the simple forms, often in a less typical manner.

Volhard suggests a three-fold classification: (1) The eclamptic type without kidney insufficiency, *i.e.*, without nitrogen and salt retention, but to be referred to edema of the brain; (2) the form with dyspeptic symptoms, twitching of the muscles and tendons, great fatigability, symptoms similar to those of urinary poisoning and associated with marked azotemia; and (3) the group including psychical disturbances, cerebral crises, transitory aphasia, paralyses, dizziness, headache, Cheyne-Stokes' breathing and nocturnal asthma.

These also are not associated with kidney insufficiency and by other authors are referred to angiospastic, arteriosclerotic, or cardiac origin and therefore designated as pseudo-uremia. It would seem that there is great advantage from a prognostic and therapeutic standpoint in classifying the manifestations of uremia into those with and without kidney insufficiency.

Treatment.—As will be seen from the foregoing, uremia is a complex condition due to different causes and associated with various conditions. This should be appreciated in the consideration of its therapy. While we recognize that these forms occur in various combinations, they frequently occur in pure types and it will be convenient to consider the treatment as applied to these types.

It is quite certain that eclamptic uremia frequently occurs independently of impaired kidney function, when it may be associated with acute glomerulonephritis, the second stage of chronic glomerulonephritis (chronic glomerulonephritis without kidney insufficiency), or with benign hypertension. Whether it is due to nephrolysins, edema of the brain, or a crystalline toxic substance, in all of the above-named conditions increased blood-pressure and slight dropsy predispose to the development of convulsions. The indications are plain and the carrying out of these is frequently followed by very gratifying results. Called to a patient developing uremic convulsions suddenly, the so-called acute uremia, the following measures should be resorted to at once:

(1) **Venesection.**—If the patient is plethoric, 500 or 600 c.c. of blood should be removed from the median basilic vein. Of course, if the patient shows evidence of cardiac weakness or is a child, much less should be withdrawn.

(2) This procedure should be followed immediately by a **lumbar puncture**. The amount of cerebrospinal fluid withdrawn will be governed by the pressure; frequently 30 or 40 c.c. will be obtained under markedly increased pressure.

(3) Thirty grains (1.95 grams) **chloral hydrate** should be administered by rectum.

If it has not already been done, **functional kidney tests** should be performed. The presence of albumin and casts are not of much help to us; they occur with convulsive seizures due to any cause. The **phenolsulphonephthalein test** should be made. Unless the output is below 40 in two hours, it is not likely that the blood urea will be increased. The "**phthalein**" test is simple and can be carried out by any physician at any place. While Marshall's method has greatly

simplified the determination of the blood urea and should be done by the physician in his office, the general practitioner usually has not the necessary equipment to do this. Usually, however, the results of both tests will be found within normal limits. The effects of these procedures are a temporary fall in blood-pressure, and a subsidence of the convulsions followed by a variable period of coma. If there is a tendency for the convulsions to return the chloral may be repeated by rectum. The author does not think that severe purgation is to be desired and has never used croton oil, which has been so frequently resorted to in these conditions.

If the patient's bowels have not moved freely, a **mild purgative** may be given. While some authors state that mercurials are contraindicated in uremia, the author's preference is for one of the mercurials. If the patient has regained consciousness sufficiently to swallow, **massæ hydrargyri**, grains 10 (.67 gram), **extractum Hyoscyami**, grain $\frac{1}{2}$ (.03 gram), may be given in capsule. If the patient is still comatose, 10 grains (.67 gram) of **calomel** may be swallowed if placed with a spoonful of snow ice on the back of the tongue. Usually there is no indication for a low protein diet, but the **salt and fluids should be restricted**. If the patient soon regains consciousness, an ordinary **light diet, salt free**, with not more than 48 ounces of fluids in the twenty-four hours, may be allowed. If unconsciousness continues for some time and nourishment be deemed necessary, one pint of a 10 per cent. solution of glucose in plain water to which 2 drams (7.8 grains) of **sodium bicarbonate** may be added can be given by proctoclysis every eight hours. If after the patient clears up, there is a recurrence of the convulsions in a few days and the patient's condition seems to contraindicate another venesection, this may be substituted by 5 minims (.3 c.c.) **tincture of Veratrum viride**, repeated as often as necessary and the other measures repeated. The further treatment will depend upon the associated kidney condition (*q.v.*).

ECLAMPTIC EQUIVALENTS.—In the course of benign hypertension and the combination form of sclerosis with nephritis, various vascular symptoms referable particularly to the nervous system and usually regarded as uremic demand treatment. As stated above, these eclamptic equivalents include transitory paralyses, disturbances in vision and hearing, paroxysmal dyspnea and Cheyne-Stokes' respiration, increased reflexes, headache and vomiting, sometimes associated with fainting attacks and psychical disturbances. Whether the transitory paralyses are to be referred to vascular crises on an arteriosclerotic basis, to localized edema, or to punctate hemorrhages or to the toxic influence associated with these, the chief indication is to lower the blood-pressure. Vasodilators have met with little success in the treatment of these symptoms. With the occurrence of transitory paralyses the patient should be put to bed and his diet limited. As a rule, the benign hypertonic is not anemic and venesection, which in these cases may be resorted to without misgivings, is one of the most valuable measures. In the cases of the combination form of sclerosis with nephritis which are more likely to be associated

with anemia and general weakness, the withdrawal of large quantities of blood will have to be more carefully considered.

The respiratory difficulties of an uremic nature, especially in the combination form, may be associated with and in part dependent upon an acidosis arising from the deficient elimination by the kidney. Mariott and Howland think that the condition may result from an increase of phosphates within the body and advocate the administration of calcium to eliminate the phosphates. In the author's experience the administration of alkalis has met with little success in the relief of these uremic respiratory symptoms. Herringham recommends strongly the **inhalation of oxygen**. **Chloral** should be tried. Usually, however, **morphin** hypodermatically will have to be resorted to. For the severe headaches often simulating migraine, and the symptoms of meningismus, the **ice-bag** and various **sedatives**, like **bromids**, **coal tar products**, and **acetyl salicylic acid** may be tried, but frequently lumbar puncture which is more likely to be attended by relief will have to be tried.

The psychical symptoms will require **absolute quiet**, a **darkened room**, and sedatives. It may be necessary to protect the patient against himself by careful watching or the restraining sheet may have to be used. **Veronal** and **trional** singly or combined will often induce sleep. A prolonged course of **erythol tetranitrate** has been recommended in melancholia with high blood-pressure as well as for the insomnia associated with this.

UREMIA WITH KIDNEY INSUFFICIENCY.—True Uremia.—This form of uremia is usually associated with the end stage of chronic glomerulonephritis and the combination form. As Janeway has stated, the treatment of the severest renal insufficiency is purely symptomatic and not a cheerful duty. While we know nothing definite about the toxin or toxins which are responsible for the symptoms of true uremia, we know that they are associated with the retention of waste products of nitrogenous metabolism in the blood and the inability of the kidney to concentrate; further, that with the retention of these products the symptoms of uremia may be prevented for a long time by a compensatory polyuria. The main indications are therefore to lower and maintain as nearly as possible the normal level of the end products of nitrogenous metabolism, represented chiefly by the non-protein nitrogen, urea, and creatinin in the blood, and to maintain the compensatory polyuria. It has been shown that the first indication may be met with some measure of success by lowering the protein intake and sparing the body protein by a high carbohydrate diet. The second indication is to be met by increasing the fluid intake, which will be successful in proportion to the reserve strength of the kidney left.

The intense anorexia and dyspeptic symptoms usually present as well as the stuporous or comatose condition of the patient may render the administration of any diet and fluid by mouth difficult. The author has found the **low protein high carbohydrate diet of Chace** most useful in these severe uremias. It calls for the juice from one lemon, two-thirds of a cup of water, one teaspoonful of cane sugar, and six table-

spoonfuls of lactose, four times a day. This will furnish about 1242 calories, approximately .8 gram of iron and an alkaline ash. Chace states that a patient can maintain himself on this diet three or four days without drawing on his body protein. After this, or before if possible, the above diet may be **substituted by the following**: Morning and evening 300 grams of ripe bananas and 100 c.c. cream; at noon 200 c.c. plain cream soup, 300 grams of bananas and 200 c.c. milk. This affords 1335 calories, 29 grams of protein or approximately 45 grams of nitrogen and an alkaline ash. Care should, however, be taken not to continue these very low diets too long because the strength of the patient will require protection, as marked asthenia is one of the chief features of this form of uremia. If the condition of the patient is such that the diet cannot be taken by mouth, 10 per cent. glucose may be administered by proctoclysis. Frequently, however, this cannot be retained per rectum, in which case it may be administered by **stomach tube**. It has long been recognized that a marked diminution of the quantity of urine in chronic nephritis without an increase in specific gravity is a forerunner of uremia. More recently Foster has shown how an increased water intake will increase the elimination of nitrogenous products. Still, Schlayer's observation that in nephritis the kidney may become fatigued when overstimulated and instead of responding with an increased diuresis may answer with diminished elimination, must not be forgotten. It is due to this fact chiefly that the more stimulating diuretics are contraindicated in his condition. However, it is desirable that with the low protein high carbohydrate diet, 2500 or 3000 c.c. of water or fluids should be taken in the twenty-four hours. This may be taken in the form of pure water or ades by mouth, or soda, glucose or saline solutions by rectum. Cardiac embarrassment is the chief contraindication to these measures.

Venesection is to be used here only after careful consideration of all the conditions present. On account of the anemia and weakened condition of the patients usually present, the ultimate harm which results will usually outweigh the immediate beneficial results. It has been proposed to overcome the undesirable results of venesection by blood transfusion or plasmaphoresis. Whether transfusion meets the difficulties has seemed questionable to the author, and he has obtained the impression that the severe reaction which frequently attends the citrate methods adds increased difficulties. Plasmaphoresis has so far met with little success. Elimination through other channels as by the bowel and skin is a time-honored indication in the treatment of uremia. Discretion is, however, to be used in the application of these measures also, as severe purgation and diaphoresis in the presence of the impaired function of the kidney may increase the concentration of the blood and increase the danger. Sufficient bowel movements may be secured by the administration of **compound Jalap powder**, dram $\frac{1}{2}$ to 1 (2 to 4 grams), which may be supplemented by **irrigation of the colon with water** at 110° F. (43.33° C.). **Diaphoresis**, the beneficial effects of which are

purely empirical, may be secured by the hot air bath, the brick method, electric light baths, hot packs and hot baths.

The severe gastro-intestinal symptoms which usually accompany this form of uremia are generally central or eliminative in origin and are best met by **lavage of the stomach and bowels** and general sedatives. Severe abdominal pain will sometimes require the hypodermatic administration of morphia. Associated conditions such as myocardial insufficiency and acidosis demand appropriate treatment. The uremia associated with obstruction of the lower urinary tract is best treated by the method of Young which consists of the introduction of a **retention catheter**, forced water intake up to 3 to 6 liters (3.17 to 6.34 quarts) per day and a low protein diet, followed by the **removal of the obstruction surgically**.

NEPHROPATHIES OF CIRCULATORY ORIGIN

The diseases of the kidneys of circulatory origin include anemia, hyperemia, embolism, thrombosis, and infarction of the kidney and arteriosclerotic processes of the kidney vessels.

The clinical symptoms and anatomical appearance attributable purely to anemia of the kidneys are so rarely encountered that it will be unnecessary to say more than that the condition occurs as a part of a general anemia from local causes which prevent an ingress of blood to the kidneys, and from spasmodic contraction of the arterial wall.

Active hyperemia of the kidney manifests itself clinically by backache, pollakiuria, and the passage of a small amount of urine which may contain albumin and a few casts. Independent of acute glomerulonephritis which it always accompanies, it may occur under a variety of conditions, as in acute infections, prolonged fevers, as a result of chilling of the body, and the irritant action of many drugs, as mercury, arsenic, antimony, potassium chlorate, turpentine, cubeb, capaiba, and cantharides.

Large hemorrhagic infarcts which result from the plugging of the renal vessels rarely occur. They may give rise to suddenly occurring hematuria accompanied by unilateral pain. The hemorrhage usually quickly disappears. These symptoms ensuing on the presence of heart disease will suggest the diagnosis.

More or less diffuse atherosclerosis of the small blood-vessels of the kidney will be described under the genetic term Bright's Disease. Chronic passive congestion of the kidneys and the focal atherosclerotic nephropathy will be described more fully here.

CHRONIC PASSIVE CONGESTION OF THE KIDNEYS

(Stasis Kidney)

Definition.—The clinical history and physical findings will depend upon the causative disease producing the myocardial insufficiency, the obstruction of the inferior vena cava above the renal veins or the ob-

struction of the renal veins themselves. Chronic passive congestion of the kidneys is most frequently associated with myocardial insufficiency which may be due to organic disease of the heart itself or to disease elsewhere in the body, to which the disturbance in the heart is secondary, *e.g.*, pulmonary emphysema, hyperthyroidism, atherosclerosis and the chronic nephropathies.

Etiology.—Experimental works show the presence of two factors in the production of chronic passive congestion of the kidneys. The *feeble* arterial flow produces cortical and glomerular congestion and exudation of albumin into the capsule and lessened venous outflow produces engorgement of the medulla.

Symptomatology.—The cardiac decompensation may be *relative* or *complete*. In the former there will be shortness of breath which is brought on by exercise or it may occur after a heavy meal and is frequently associated with the excessive use of tobacco. The dyspnea frequently manifests itself in asthmatic attacks at night and is due to the more or less complete edema of the lungs which results from the early failure of the left ventricle in conditions like aortic regurgitation, sclerosis of the coronary arteries, benign hypertension, and sclerosis of the kidney vessels combined with nephritis. Cough is frequently present and may occur in paroxysms. A feeling of constriction in the chest, which sometimes amounts to pain, may be complained of. Certain movements of the body may produce dizziness. If carefully looked for, edema about the ankles may be discovered, and the patient not infrequently complains of edema in this area occurring during the daytime which disappears after a night's rest. Cyanosis may be present. Disturbances in sleep are common. The sleep is restless and disturbing dreams and nightmares frequently awaken the patient.

The symptoms of complete cardiac decompensation are more outspoken. The dyspnea is more severe and is present when the patient is at rest. While the mechanism of dyspnea in cardiac disease is not well understood, several causative factors have been suggested, as insufficient ventilation of the pulmonary alveoli, insufficient interchange of gases between the blood and the air in the alveoli, and retardation of the blood flow in the tissues and acidosis. Insufficient ventilation of the pulmonary alveoli is favored by several conditions which may be associated with or the result of cardiac decompensation, *e.g.*, pulmonary congestion, bronchitis, bronchopneumonia, pulmonary infarction, the enlarged heart, pericardial and pleural effusions, and interference with movements of the diaphragm by an enlarged liver or ascites. Von Basch attributed cardiac dyspnea to increased lung volume and diminished elasticity of the pulmonary tissue. Modern studies have, however, shown that there is no increased volume inasmuch as the residual air in cardiac decompensation is normal or only slightly increased and the mid volume of air is less. Still the diminished elasticity is shown by the diminution of the vital capacity which may be only 20 or 25 per cent. of the normal in these cases. Siebeck has called attention to the fact that ventilation is rendered more difficult by the fact that a large

proportion of the inspired air is breathed out with the next expiration. The same author also found that the functional dead space is increased in heart disease. It has often been assumed that an insufficient interchange of gases between the blood and the air in the alveoli is a factor in cardiac dyspnea. Hürter has, however, shown that the oxygen of the arterial blood in cases of cardiac decompensation is over 80 per cent. of the normal capacity, and Hewlett suggests that the retardation of the blood flow through the tissues which results in an inadequate supply of oxygen to the tissues or inadequate removal of carbon dioxide from them is a more important factor in the production of dyspnea.

Lewis and his co-workers have called attention to the frequent association of cardiac insufficiency with acidosis which probably is renal in origin. Hewlett believes that while acidosis may be a contributing factor in the production of cardiac dyspnea, it is not the sole or the chief factor for the following reasons: (1) The degree of acidosis is rarely extreme; (2) equally marked degrees of acidosis in diabetes cause hyperpnea without dyspnea; (3) the administration of sufficient alkalis to cause an alkaline urine does not usually relieve the dyspnea to any material degree; and (4) no definite relation exists between the degree of dyspnea and the degree of acidosis.

Frequently patients with complete cardiac decompensation breathe better sitting up than in the recumbent posture, a condition designated as orthopnea. The sitting posture lowers the abdominal viscera which push out the anterior abdominal wall, thereby producing more favorable conditions for expiration. It also lowers the position of the diaphragm which increases the size of the lungs as well as the aperture traversed by the inferior vena cava, thereby favoring the return flow of blood from the lower parts of the body. In complete cardiac decompensation the cardiac asthma of relative insufficiency usually gives place to a stasis bronchitis. Though in complete decompensation paroxysmal attacks of difficult breathing frequently occur and are often associated with Cheyne-Stokes' breathing, McKenzie is disposed to look upon Cheyne-Stokes' breathing as the origin of cardiac asthma in all cases.

Cough is a frequent symptom of myocardial insufficiency. It may be nonproductive when it may be due to pressure of an enlarged left auricle on the recurrent laryngeal nerve. It is, however, more frequently productive when it may be due to several associated conditions as edema of the lungs, stasis bronchitis, bronchopneumonia, or pulmonary infarction. The character of the sputum will vary according to the associated condition. In edema of the lungs there is a large quantity of frothy serous sputum which may be tinged with bright red blood; in bronchitis and bronchopneumonia it may be mucoid or mucopurulent; in mitral disease it is frequently hemorrhagic, when it is due to capillary rupture and the patient frequently experiences a sense of relief; in pulmonary infarct it is dark red, prune-juice in character, and the symptoms, instead of being relieved, are frequently exaggerated.

Under normal conditions no notice is taken of the heart's action, but under a variety of abnormal conditions this is forced upon the conscious-

ness of the patient, and is usually spoken of as palpitation. This frequently occurs independently of myocardial insufficiency, but is often associated with various forms of arrhythmia as with premature contractions, auricular fibrillation and the nodal rhythm associated with paroxysmal tachycardia.

Severe pain is not a prominent feature of decompensation. Sir Clifford Allbutt has pointed out that the term "anginal" has been rather loosely used in recent medical literature. The character of the pain in decompensation is rarely that of true angina pectoris. It is not severe or paroxysmal, is not attended by the peculiar dread of angina and the radiation is usually absent or little characteristic. It is rather submammary in location and of a dull aching character like the "heart ache of melancholia" and may be regarded as "a remonstrance of an overworked, engorged, inflamed, underfed, or decaying organ." It may be associated with hyperesthesia in the mammary region and with tenderness of the left sternocleidomastoid and trapezius. It rarely may assume a true anginal character in association with mitral stenosis, sudden embolism and pericarditis.

Cyanosis, a bluish or deep purple discoloration of the acral parts of the body and mucous membranes, is not infrequently present. It is due to the marked reduction of oxyhemoglobin to hemoglobin which is favored by venous obstruction which produces slowing of the blood stream and dilation of the superficial vessels.

Icterus is not uncommon. It may be due to catarrh of the bile ducts, hepatic congestion, or to gall-stones which are not infrequently associated with cardiac disease.

The edema of myocardial insufficiency has several characteristics which differentiate it particularly from the edema of nephrosis. It tends to occur first in the most dependent parts of the body. When the patient is up and about it appears first in the lower extremities; when the patient is recumbent, on the posterior surfaces of the body; or if the patient lie long on one side, the lower arm may be more edematous. While in severe cardiac decompensation most of the subcutaneous tissues of the body may take part in the edema, the scalp is rarely involved in cardiac edema. The serous cavities quite frequently contain fluid. Ascites from back pressure may be great. Effusion into both pleural cavities may occur, although the right is more apt to contain fluid in greater quantity when it is present in both sides. The hydrothorax of nephrosis is more likely to be bilateral. The increased tendency to right hydrothorax in cardiac disease was formerly explained by pressure of the dilated right heart on the root of the right lung indirectly pinching the major azygos vein as it curves over the root of the right lung to enter the superior vena cava. Fetterolf and Landis, however, present good evidence to show that the effusion comes from the visceral layer of the pleura and that it is due to the pressure of the dilated auricles on the pulmonary veins. The greater frequency in the right side is due to the fact that the dilatation of the right auricle is more common and more easy than a similar condition of the left side. No satisfactory explana-

tion has been offered for the vagaries of cardiac edema—why it occurs in some cases and not in others or why it may sometimes be present in the serous cavities and absent in the subcutaneous tissues. The edema fluid of cardiac origin does not present the pseudochylous appearance of the edema of nephrosis. In cardiac edema the total protein content is greater; the ratio of albumin to globulin and the percentage of globulin in protein are much less. While the mechanical factors such as increased pressure in the veins and capillaries, slowing of the blood stream, and the interference with the lymph flow play an important part in the production of the edema of heart disease, it would appear that injury of the vessel wall from toxic, vasomotor, bacterial, or metabolic influence is also necessary. An hydremic condition of the blood may be an additional factor. As a result of chronic passive congestion, there is an overfilling of the blood-vessels of the alimentary tract and consequent impairment of the organs of digestion. Anorexia and indigestion result and, in marked failure of the right side of the heart, may be extreme.

The chemism and motility of the stomach are impaired, and as a result the food undergoes fermentation with the production of flatulence, which further embarrasses the heart's action.

Vomiting may be extreme in the late stages of decompensation. Its mechanism is not clear. It is usually associated with left-sided heart failure and may be attributed to deficiency of blood supply to the medulla and a stimulation of the vomiting center. It may, however, be the result of reflex stimulation of the vomiting center by means of afferent impulses from the stomach through the vagus.

By the same mechanism, meteorism arises in the intestines, and the decreased secretory activity and the diminished motility produce constipation which is often present. On the other hand, the edema may be great and the irritation so marked that diarrhea may result.

Hemorrhoids are frequently present as a result of portal obstruction.

Pain in the abdomen not infrequently occurs in myocardial insufficiency. It varies in character and mechanism. A dull aching pain in the epigastrium increased by pressure and the ingestion of food is often present as a result of the swollen congested liver. More severe pain may be caused by embolism of the spleen or intestines.

Psychical symptoms are common in cardiac decompensation. Insomnia, mania, and unconsciousness as a result of insufficient blood reaching the brain may occur. Stupor and drowsiness are less common.

PHYSICAL FINDINGS.—In relative myocardial insufficiency, the physical findings will depend upon the causative disease. Most frequently there will be hypertrophy of the left ventricle with beginning dilation. One of the first signs of failure of the left ventricle will be the presence of râles over the bases of the lungs posteriorly. If the ventricle becomes much dilated there will be the signs of relative mitral insufficiency. The rhythm of the pulse before failure of the right ventricle is remarkably good, though extrasystoles may be present. In cases dependent upon renal hypertension, presystolic gallop rhythm is quite common.

In complete decompensation the heart is dilated as shown by the diffuse wavy apex beat, the widening of the area of cardiac dulness to the left and right, blurring and softening of the heart sounds, blowing murmurs of relative mitral insufficiency, and less commonly of tricuspid insufficiency. Now marked disturbance of rhythm appear, premature contractions, auricular fibrillation, pulsus alternans, tachycardia. Pulse deficit is also often present. There is engorgement of the veins of the neck and a systolic venous pulse may be made out. Over the bases of the lungs, there is impaired resonance, diminished breath sounds and crackling râles as well as frequently signs of fluid in the pleural cavities. Areas of consolidation, over which there is a pleuritic friction rub with the characteristic sputum, indicate hemorrhagic infarction. In the abdomen, the liver will be found enlarged and tender, and frequently pulsation of same can be made out. The spleen may be palpable and the signs of free fluid in the abdominal cavity are often present.

The symptoms and signs of obstruction of the inferior vena cava will depend upon the cause of the obstruction, such as chronic mediastinitis, mediastinal tumor, increased intra-abdominal tension as by ascites or large tumor, pressure from without, without markedly increased intra-abdominal tension as by malignant tumors of the retro-peritoneal lymph spaces and by thrombosis of the inferior vena cava. Marked distention of the abdominal veins with reversed blood flow is significant.

THE URINE.—In relative myocardial insufficiency there are remarkably few changes from normal in the urine. The patient will frequently complain of nycturia and there may be a night polyuria which should not be confused with the nycturic polyuria of nephritis. That of cardiac origin will usually be associated with a day oliguria. In complete cardiac decompensation, the quantity of urine is diminished in amount; it is dark in color and shows a heavy precipitate of urates; albumin is present in varying quantity; and in the sediment there are, besides the urates and uric acid crystals, casts which may be of all kinds, and a few red and white blood-cells.

KIDNEY FUNCTION.—That the kidney function is impaired in chronic passive congestion of the kidney may be shown both clinically and experimentally. The impairment varies according to the condition, *i.e.*, according to the stage of the decompensation or whether the chronic passive congestion is superimposed on a nephritis.

The response to the Mosenthal kidney test-meal in long-standing relative myocardial insufficiency and in the stage of edema of complete decompensation shows the following:

- “(1) A fixed specific gravity at about 1020 in the day urine.
- “(2) Diminished output of salt. The low percentage of figures for salt are outspoken.
- “(3) An adequate nitrogen output. The very high concentration of nitrogen is in marked contrast to that of salt.
- “(4) An oliguria.
- “(5) A normal night urine.”

During the stage of the elimination of edema there will be the following:

- “(1) A low and somewhat fixed specific gravity.
- “(2) Nitrogen elimination normal.
- “(3) The salt and water excretion exceed the amount ingested.
- “(4) The night urine is increased and has a low percentage of nitrogen.”

After the elimination of edema, the following results may be obtained:

- “(1) A low moderately fixed specific gravity.
- “(2) Normal nitrogen and water output.
- “(3) Slightly diminished salt excretion.
- “(4) The night urine may or may not be increased in quantity; its specific gravity and nitrogen concentration are low.”

In myocardial insufficiency associated with chronic nephritis the results may exhibit the characteristics of either lesion; usually, however, the chronic passive congestion proves itself the predominating feature (Mosenthal). The phenolsulphonephthalein output may be markedly lowered in pure chronic passive congestion or that associated with nephritis. When low renal function is followed by an increased phthalein output, the amount of increase gives a fair approximation of the extent of cardiac decompensation. In pure passive congestion the non-protein nitrogen very rarely shows an increase above 50 mg. per 100 c.c. of blood. A phthalein rapidly returning to normal, associated with a low level of blood urea, speaks strongly for passive congestion as the underlying factor.

In pure passive congestion, Ambard's coefficient is rarely above .15. This rapidly falls to normal with return of compensation (Rowntree).

The diagnosis of pure passive congestion and that associated with nephritis may be made by a consideration of what has been stated with reference to the clinical history, physical findings, and functional conditions which need not be repeated.

Treatment.—The indications for treatment are offered by the underlying cause. This is usually the myocardial insufficiency and the measures to be carried out are much the same whatever may be the cause of this. **Rest**, absolute in bed when possible, should be insisted upon. If the dyspnea is great, the patient may be more comfortable on a **back rest**, or in the severest cases the position most comfortable to the patient may be allowed. The rest should be continued until the serious manifestations disappear. In the chronic cases and those with partial decompensation, the patient may be allowed to be wheeled in a chair into the open. The **diet** requires careful supervision. The quantity of food in the meal and the number of meals should be given attention. It is much better to order small amounts of food in five feedings per day than larger meals three times a day. The salt and fluid intake must be markedly restricted. In severe cases of myocardial insufficiency the **Karell diet** is attended by its most brilliant results. This consists of 200 c.c. of milk four times a day and nothing else. After four or five

days, or in less severe cases, the author has found Rowntree's modification of this diet excellent:

- 9 A. M.—200 c.c. of milk (1/3 pint).
 1 shredded wheat biscuit.
 1 egg, soft boiled or poached.
 1 slice of bread, salt free.
 1 butter ball, salt free.
- 1 P. M.—Soup (chicken or tomato), 200 c.c., no salt.
 Lamb chop, 100 grams (.3 lb.), or chicken 150 grams (.4 lb.).
 Mashed potatoes, 100 grams (.3 lb.).
 1 soda cracker, salt free.
- 5 P. M.—Milk, 200 c.c.
 1 egg, soft boiled or poached.
 1 slice of bread, 40 grams, salt free.
 Rice, or tapioca pudding, 100 grams (.3 lb.).
- 9 P. M.—Milk, 200 c.c.
 1 A. M.—Milk, 200 c.c.
 5 A. M.—Milk, 200 c.c.

The fluids should be restricted according to the amount of edema present. At first the total quantity should rarely exceed 1000 or 1500 c.c. It is practically impossible to arrange a salt-free diet; in severe cases where the salt concentration in the urine is low, no salt at all should be added. With improvement in the salt concentration, the salt may be carefully added. It is surprising how rapidly the edema disappears and the heart improves under these measures. Other methods, such as depletion, support of the heart, diuretics, and symptomatic treatment must not be neglected and frequently will be necessary. In acute dilation of the right heart with severe orthopnea, **venesection** may be necessary even in the presence of anemia. The quantity of blood withdrawn will depend upon the condition present. If the hemoglobin percentage is not very low, below 70 per cent., 400 to 600 c.c. should be removed; if lower it will probably be better to remove smaller quantities. If the patient has not previously had **digitalis**, **amorphous strophanthin**, grain 1/200 (.00032 gram), or better, **ouabain**, in one-half the dose, may be administered intramuscularly. The local disagreeable effects may be overcome by local massage for fifteen minutes. If the accumulation of fluid in the serous cavities produces disagreeable effects, it should be removed by **paracentesis**. It is also desirable to secure free bowel movements. **Magnesium sulphate**, 1/2 ounce (16 grams), one or two **compound cathartic pills**, **compound jalap powder**, grains 30 (1.95 grams), or **eletarin**, grain 1/20 to 1/10 (.00324 to .00648 gram) may be given. It is the author's belief that in complete cardiac decompensation, whatever the cause—whether the heart is rapid and fibrillating, or the rhythm is normal, or whether chronic diffuse glomerulonephritis, benign hypertension or the combination form is present—**digitalis** is indicated. The essentials in its administration are the knowledge of an active preparation, the symptoms of its toxic effect, and the pushing it to its therapeutic effect. Given standardized leaves, the tincture or infusion in doses equivalent to grains 1 1/2 (.0974 gram) of the leaves may be given every four hours, for forty-eight hours. The

author prefers **digipuratum**, now known as **digitan**, the tablets of which represent $1\frac{1}{2}$ grains (1.0974 gram) of the standardized leaves. If the desired diuresis does not result, the **cafein diuretics** will be valuable aids. These are best administered according to the method of Romberg's clinic—**cafein citrate**, grains 2 (.13 gram), **diuretin**, grains 10 (.65 gram), or **theocin**, grains 3 (.195 gram), may be given and repeated for three doses. These should not be repeated until their diuretic effect begins to subside. A diminishing quantity of urine, the occurrence of a pulse of 60, an abnormal rhythm, especially a bigeminal pulse, or nausea, vomiting, or headache are the indications for stopping the digitalis. The continuance of this drug in the so-called chronic digitalis treatment will depend upon the character of the case.

SYMPTOMATIC TREATMENT.—The edema will be controlled, if at all, by rest, restriction of fluids and salt, paracentesis, digitalis, and the **cafein derivatives** as described above.

For the dyspnea, it will be desirable to determine the cause and remove it if possible, control flatulence by proper attention to the diet, the use of the back rest, the administration of **morphin** and **atropin**, and venesection followed by **strophanthin** may be necessary.

Palpitation and cardiac distress may usually be overcome by attention to the gastro-intestinal tract and the application of the **ice-bag** or **small blisters over the precordium**.

The gastric symptoms may be the result of digitalis or purgatives and if so, these should be withdrawn as well as all food for twelve hours and gastric sedatives given internally with the application of counter-irritants over the epigastrium.

Cough will usually respond to the general measures described above without the necessity of expectorant mixtures.

Hemoptysis may occur and requires insistence on absolute quiet and the use of the ice-bag.

Edema of the lungs occurring acutely and severely may sometimes be relieved by morphin, but sometimes venesection combined with morphin will be life-saving in this condition.

Insomnia will often require the back rest and the administration of sedatives and hypnotics.

Pathology.—Macroscopically the kidney will usually be found somewhat enlarged, of an extreme rubbery consistency, and of a deep purplish gray color. The surface is smooth and the capsule is not adherent; on cut section, the color is gray purplish and striations are quite distinct. In the cortex, the glomeruli and blood-vessels show red and the tubules gray. The pyramids are deeply reddened.

Microscopically the glomerular loops are distended with blood. Coagulated fluid may be found in the capsular space and casts in the tubules. The tubular epithelium may show cloudy swelling. The interstitial connective tissue may be increased, but usually is not much in evidence, the hardness being due to the distention with blood.

THE FOCAL ATHEROSCLEROTIC KIDNEY

(*Senile Arteriosclerotic Kidney, Decrescent Arteriosclerotic Kidney*)

Symptomatology.—CLINICAL HISTORY.—The symptoms of focal atherosclerotic kidney are those of senile or decrescent arteriosclerosis in which it occurs as a part of the general process. They are usually gradual in onset, and, as expressed by Sir T. Clifford Allbutt, are for the greater part negative and consist in a drought of the body, in failing irrigation of the organs such as the cardiac, the renal, the cerebrospinal, the gastro-intestinal, and the rest. The withered skin, the shrunken limbs and the shuffling gait may be noted, or the onset may be more rapid, the result of premature old age, and the symptoms may be those of progressive cachexia with pallor and emaciation.

The blood-pressure is not increased, rarely transitory rises may be noted, and the heart is not hypertrophied. The symptoms which will be found to form such a prominent part of the clinical history of benign hypertension are conspicuous by their absence.

Dyspnea may be present as a result of emphysema which so frequently occurs in this condition. There may be anorexia, loss of flesh, hypochlorhydria or achlorhydria which, with hematemesis sometimes occurring as a result of local atrophy dependent upon atherosclerosis of the gastric vessels, awaken the thought of carcinoma of the stomach. From the same lesions in the intestinal vessels, flatulence, melena, and other intestinal symptoms may be present. Sclerosis of the pancreatic vessels may be attended with markedly fatty stools and a trace of sugar in the urine. Severe abdominal pain from spasm and cramp in the intra-abdominal vessels is not a feature of senile arteriosclerosis.

The cerebral palsies of decrescent arteriosclerosis are atrophic rather than hemorrhagic in nature. They result from a lacunar process, irregular cavities being formed by areas of atrophic softening, or from thromboses, the formation of which are favored by the arteriosclerotic cerebral vessels. Rarely, hemiplegia from cerebral hemorrhage may occur as the result of the transitory hypertension which sometimes comes on in these cases. Severe and profound melancholia, associated not only with obsessions but delusions, may occur. Garrulity, tearfulness, loss of memory, disorders of sleep, especially insomnia in the early morning, are familiar symptoms of senile arteriosclerosis.

The eye-grounds may show changes which are more likely to depend upon degeneration due mainly to deficient nutrition than to edema.

PHYSICAL FINDINGS.—The general appearance has already been referred to. The visible and palpable arteries will usually show marked arteriosclerotic changes. The beaded, tortuous arteries are much more frequent in this condition than in benign hypertension. The heart does not show evidence of hypertrophy, though a systolic murmur at the apex may be present as the result of atherosclerotic processes in the mitral valve. There may be hyperresonance with prolonged expiratory sound as the result of emphysema. The reflexes may be increased.

LABORATORY FINDINGS.—The urine shows slight or no abnormal changes—a trace of albumin, a few hyalin casts and red blood-cells may be found in the centrifuged specimen. The blood often shows a mild secondary anemia.

The functional capacity of the kidneys is very little affected in the senile arteriosclerotic kidney. The results of the concentration tests, the phenolsulphonaphthalein excretion, and the figures for non-protein nitrogen and urea in the blood are within normal limits.

Treatment.—As Sir T. Clifford Allbutt says, “Decrescent arteriosclerosis is **immedicable**. We cannot hold time by the wings, and with some men it flies faster than with others.” The mild degrees of increased pressure which belongs to advanced age should not be interfered with. Those cases showing marked transitory rises of pressure should receive the treatment of benign hypertension. The quality of the blood may be improved by mild alteratives, mild baths, moderate exercise short of fatigue in the open, by careful attention to the excretory organs, and by **ferruginous tonics**.

Pathology.—The kidneys may be normal, slightly enlarged, or slightly reduced in size. They are firmer than normal. There may, in various areas on the surface of the kidney, be depressions corresponding to localized or patchy atrophy due to arteriosclerosis of vessels supplying the part. These usually produce rather large areas of unevenness since here it is the larger vessels which are involved in the atherosclerotic process. On microscopical examination there will be found the evidences of atherosclerosis of the larger vessels with atrophy of the areas supplied by these while the other portions of the parenchyma will be found intact.

THE NEPHROPATHIES GENERALLY INCLUDED UNDER THE GENETIC TERM BRIGHT'S DISEASE

Introduction.—The term, Bright's disease, in its original significance included diseases of the kidney associated with albuminuria and dropsy. To-day it is used in a much broader sense and includes a variety of degenerative, inflammatory, and atherosclerotic processes in the kidney to which the term nephritis has been applied clinically. These conditions have usually been described in text-books under the heads of acute parenchymatous nephritis, chronic parenchymatous nephritis, and chronic interstitial nephritis. It has been difficult to arrive at a classification of these nephropathies equally satisfactory to the clinician and the pathological anatomist because there has been no harmony as to the pathogenesis of the various forms.

On the pathological side, it has been questioned whether there is such a thing as parenchymatous inflammation as applied to the kidney. Lubarsch states that it is impossible to differentiate whether there is a progressive or a regressive process in a cell in the stage of cloudy swelling; further that if one holds that inflammation must always be a progressive process, one must discard the idea of a parenchymatous in-

flammation. Ribbert holds that the epithelium does not inflame and that all regressive processes must be excluded from the picture of inflammation. He further holds that inflammation is an accompaniment and not the fundamental cause of the disease process, that the disease-producing process is always found in the regressive parenchymatous changes to which the inflammation is secondary. Ribbert thus accepts the view of Weigert that every inflammation is produced by a parenchymatous lesion; he would speak only of acute, subacute, and chronic nephritis and reserve the name nephrosis for those lesions which are only of a degenerative nature. Löhlein has, however, shown that a large number of cases which were earlier designated as chronic parenchymatous nephritis arises from chronic glomerulonephritis, therefore from cases in which the parenchymatous degeneration did not precede the inflammatory changes in the glomeruli, but in a great measure was produced by them. On the other hand, Aschoff holds to the view of a parenchymatous inflammation, emphasizing the nature of the inflammatory process as a reaction to an injury, which as Adami states is adaptive in character. Aschoff emphasizes that up to cell death there are all possible transitions, that, in any case, a stage precedes cell death in which the cell is swollen, excretion increased, therefore showing active manifestations of life. In acute hematogenous diseases of the kidney, Aschoff differentiates degenerations, dependent upon disturbances of metabolism (amyloid, system necroses in poisoning), and those which show changes based on circulatory disturbances—inflammation with predominating reactions in the vascular connective tissue (nephritis exudativa serosa, nephritis exudativa purulenta, nephritis interstitialis acuta), and inflammation with predominating reaction in the filtration and secretory apparatus, nephritis tubularis (parenchymatous inflammation), glomerulonephritis, and a mixed form of tubular and glomerular nephritis.

Volhard, using increased blood-pressure as the clinical indication of the presence of an acute, subacute, or chronic nephritis, found that the old clinical syndrome expressed by the term chronic parenchymatous nephritis included two groups of cases which differentiated themselves by the condition of the blood-pressure. In the group without increased blood-pressure, there was found at autopsy, macroscopically, the large white kidney. Yet microscopical examination of these kidneys failed to show any evidence of inflammatory changes—hyperemia, stasis, exudation, proliferation—but evidence of certain forms of degeneration of the epithelium of the kidney tubules; while in the group with increased blood-pressure, these evidences of inflammation were present in the glomeruli. Fahr, however, has shown that later in these cases there may be evidence of a secondary inflammatory process in the interstitial tissue, that indeed, in the final stage of these kidneys a markedly contracted kidney may occur as the result of replacement fibrosis without manifestations of inflammation in the glomeruli.

In the course of further clinical and anatomical investigation, it was found that true inflammatory processes may occur in the kidney with the absence of increased blood-pressure. These cases included a

group of hemorrhagic focal nephritides, such as the embolic focal nephritis of Löhlein, occurring chiefly in streptococcic viridans sepsis, the acute interstitial focal nephritis described by Reichel and Councilman, as occurring after scarlet fever and septic processes, and the focal glomerulonephritis which also occurs in septic processes like scarlet fever, angina, etc.

It was also found that the so-called interstitial indurative nephritis did not represent a single entity. The work of Jores, Fahr, Gaskell, and others, has shown that these kidneys are not the outcome of a gradual interstitial inflammation, but that they are primarily due to arteriosclerosis of the small and smallest blood-vessels of the kidney. This group is characterized by high blood-pressure and cardiac hypertrophy, but the condition of the kidney function served to show that here are two subgroups: the one without disturbance of kidney function which Volhard and Fahr designate as benign hypertension, which Janeway called hypertensive cardiovascular disease, and which Clifford Allbutt speaks of as hyperpiesis; the other with disturbance of kidney function designated by Volhard and Fahr as malignant hypertension, the combination form—arteriosclerosis plus nephritis.

It therefore appears that the old terms, parenchymatous and interstitial, with which there has been painful disagreement between the clinical and anatomical diagnoses, had best be discarded, and the classification of these nephropathies approached from the clinical, functional and anatomical standpoints, which offers advantages for diagnosis, prognosis and treatment. The classification of Volhard and Fahr which the work of other observers has tended to confirm seems best. They with F. von Müller designate the degenerative nephropathies as nephroses, the inflammatory as nephritides, and the arteriosclerotic processes as scleroses, and suggest the following classification:

- A. Degeneration diseases: *Nephroses*, genuine and of known etiology, with and without amyloid degeneration of the vessels.
 - (1) Acute course.
 - (2) Chronic course.
 - (3) End stage: Nephrotic contracted kidney without increased blood-pressure.
- B. Inflammatory diseases: *Nephritides*.
 - (1) Diffuse glomerulonephritis with obligatory increased blood-pressure, course in three stages:

<ol style="list-style-type: none"> (a) Acute stage (b) Chronic stage without kidney insufficiency. (c) End stage, with kidney insufficiency. 	{	All three stages may run a course <ol style="list-style-type: none"> (a) Without edema. (b) With edema, i.e., with marked and diffuse degeneration of the epithelium.
---	---	--
 - (2) Focal nephritis, without increased blood-pressure.
 - (a) Focal glomerulonephritis.
 1. Acute stage.
 2. Chronic stage.
 - (b) Septic interstitial nephritis.
 - (c) Embolic focal nephritis.
- C. Arteriosclerotic diseases: *Scleroses*.
 - (1) Benign hypertension—pure sclerosis of the kidney vessels.
 - (2) Malignant hypertension—the combination form, genuine contracted kidney—sclerosis plus nephritis.

NEPHROSIS

(*Degenerative Nephropathy, Parenchymatous Nephritis, Tubular Nephritis.*)

Definition.—Under the term nephrosis, the pathologist includes all degenerative lesions (cloudy swelling, granular and fatty degeneration, and necrosis) of the kidney in which the inflammatory lesions are not above suspicion. Cloudy swelling, designated pathologically as the first stage of nephrosis, gives rise to no symptoms other than albuminuria and cylindruria, while necrotic lesions give rise to a special symptomatology which will be described under necrotizing nephrosis as represented by the sublimate kidney.

The clinical picture to be described includes the forms heretofore known as chronic parenchymatous nephritis without increased blood-pressure, and represented by kidneys showing granular degeneration and fatty degeneration of the epithelium of the tubules without inflammatory changes in the glomeruli.

Etiology.—The nephroses occur much less frequently than other nephropathies. Volhard and Fahr had 55 cases among 565 cases of Bright's disease. The author saw 10 cases in about 100 cases of the nephropathies. The degenerative lesions of the kidney may be divided into two groups with respect to etiology. In the first group, which includes the purest and most typical cases, no cause can be discovered. These have been called genuine nephrosis. There is, however, some evidence to show that exposure to cold and heredity may play a slight rôle as predisposing causes. Recent experimental work would also indicate that a continued high protein diet may produce degenerative lesions of the kidneys in rabbits which are similar to those found in the kidney in human cases of nephrosis. Newburgh states with reference to these lesions that "the lesion is not the result of arteriosclerosis, for the arteries are not diseased. Nor are we dealing with a primary glomerulonephritis. Judging by the constancy and severity of the damage to the epithelium of the convoluted tubules, the firm impression is gained that the offending substance has the primary and chief deleterious effect upon these and the slowly progressing injury of the proximal convoluted tubules is accompanied by an overgrowth of connective tissue." While Newburgh does not claim this for his sections, the author thinks they are strikingly like those described and pictured by Fahr for the various stages of nephrosis, i.e., from cloudy swelling through the stage of demonstrable lesions in the epithelium and inflammatory reaction in the connective tissue to the end stage of nephrotic contracted kidney.

In the second group, which are more frequent, are those cases which are the result of known causes. These are the toxins of infectious agents, endogenous toxins and the toxic action of various metals.

INFECTIOUS AGENTS.—Why the toxins of bacteria when acting on the kidney will at one time excite an inflammatory reaction in the glomeruli, at another time produce degenerative lesions in the epithelium chiefly

of the proximal convoluted tubules, or occasionally both of these lesions together, is not understood. It can scarcely be due to the difference in reaction in the vascular connective tissue and the epithelium, because there are pure cases of nephrosis and diffuse glomerulonephritis which are the result of the same cause. It has been suggested that the degenerative lesion may be the result of the specific infection and the nephritis due to a complicating streptococcus infection. Some observers have claimed that the injection of tuberculin may cause a glomerulonephritis, and it is suggested that in this instance the nephritis may be due to the tuberculin and the nephrosis due to the toxins resulting from the disintegration of tissue cells, which latter may be a factor in the production of nephrosis in other infections.

Nephrosis, according to Volhard and Fahr's experience, is most frequently associated with *tuberculosis*, especially tuberculosis of the lymph glands and bones. Fifteen of their 55 cases were ascribed to tuberculosis. In one of the author's 10 cases pulmonary tuberculosis was the only apparent cause. Munk has emphasized the importance of *syphilis* as a cause of degenerative lesions in the kidney. Volhard and Fahr had 7 cases due to syphilis among 55 cases. In 4 of the author's 10 cases syphilis was the apparent cause. *Chronic suppurative processes* are also responsible for some cases of nephrosis. All of these causes, tuberculosis, syphilis, and chronic suppurative processes, are usually regarded as giving rise to amyloid disease of the kidney, and the most of the kidney diseases resulting from these causes have been regarded as amyloid disease. But, as we shall see, the same symptoms occur with the nephroses whether they are accompanied by the deposit of amyloid substance in the kidney or not, so that the presence of amyloid is a complication which often can be diagnosed only at autopsy.

Nephrosis may rarely occur in the course of other infectious diseases such as diphtheria, typhoid fever, measles, cholera, and yellow fever. The hemoglobinuric kidney most frequently shows a degenerative lesion of the epithelium with slight or no involvement of the glomeruli. Yet the symptoms of hemoglobinuric fever rarely correspond to that of the second stage of nephrosis. The edema is usually lacking and there is frequently an increase of blood-pressure. We may have here a condition analogous to that of severe mercurial poisoning in which there is absence of edema and the presence of increased blood-pressure with marked nitrogen retention in the blood. The increased blood-pressure in both may be due to the anuria and increase of non-protein nitrogen in the blood.

ENDOGENOUS TOXINS.—The *kidney of pregnancy* which arises as the result of an intoxication of the body by the passage into the maternal circulation of ferments and autolytic products from the placenta is frequently a purely degenerative lesion of tubular epithelium. It is true that this kidney of pregnancy is also often superimposed upon an old nephritis which has existed a long time before the pregnancy; an acute nephritis may develop along with the nephrosis of pregnancy when in either case the clinical history and findings may indicate the association

of the two conditions. It is also possible that some of these cases may show increased blood-pressure and changes in the eye-grounds without inflammatory changes in the glomeruli which are at variance with the clinical history of a pure nephrosis. In such cases there may be marked vascular changes, and it is possible that these as well as the increased blood-pressure are due to the placental toxins.

Cachectic conditions which occur as the result of malignant tumors may give rise to nephrosis.

Metallic poisons may give rise to purely degenerative lesions of the kidney. Of these phosphorus, bichromate of potash and bichlorid of mercury may be mentioned. The latter is the most important from a clinical standpoint.

The table taken from Volhard and Fahr with the author's cases included will illustrate not only the etiology of nephrosis, but also the causes of the different stages of the disease.

AFTER VOLHARD AND FAHR WITH AUTHOR'S CASES ADDED

Type	Acute	Chronic	End Stage	Total
Genuine		$7 + 1 = 8$		
Pregnancy	2			
Diphtheria	7			
Tuberculosis		$15 + 1 = 16$	3	
Lues	$2 + 1 = 3$	$5 + 3 = 8$		
Chronic Suppurative		3		
Pancarditis (Viridans sepsis)		2		
Staphylococcic sepsis	1			
Measles	1			
Sarcomatosis		1		
Bichlorid of mercury	$6 + 4 = 10$			
Total	24	38	3	65

Symptomatology.—There is no period of incubation as is apparent in some cases of diffuse glomerulonephritis. The onset is gradual and insidious. The patient is rarely able to state definitely the time of beginning. The symptoms which usually take the patient to the physician are anorexia, fatigability, pallor of the skin, matutinal edema of the eyelids and edema of the feet, when upon examination a high albuminuria will be present. The skin presents a clear bluish-white color in marked contrast to the blood findings unless anemia is present as a result of the causative disease. Anorexia is present during the stage of the edema, but the appetite may later be but little impaired, even voracious. There is a marked tendency to diarrhea which may be profuse and painless especially during the edematous stage, and is probably due to the increased permeability of the blood-vessels of the intestinal tract. A marked feature is the absence of increased blood-pressure and cardiac hypertrophy except in those cases in which arteriosclerosis existed before the onset. As a rule there are no abnormal changes in the eye-grounds.

In the beginning the subjective symptoms are not prominent. The

patient may complain of fatigue, weakness and emaciation which is at first obscured by the edema. The long continuance of the disease with pitiful sameness renders the patient altogether miserable.

PHYSICAL FINDINGS.—On physical examination edema is apparent and dominates the clinical picture of the disease. It usually begins in the face and rapidly involves the subcutaneous tissues of the whole body, the external genitals and the serous cavities. Hydrothorax and ascites may be present without the generalized edema.

The edema fluid is characterized by a milky, cloudy, pseudochylous appearance, probably due to globulin-lipoid substances. The blood-serum shows the same appearance, which probably arises from the fatty kidneys, since the same double refracting lipoid substance is present in the interstitial tissue and endothelium of lymph vessels of such kidneys. The fluid is watery and poor in proteins, the albumin content, according to the Esbach test, being from .25 to .5 per cent. The nitrogen content, according to Volhard and Fahr, is from .036 to .12 per cent. and the sodium chlorid concentration the same as that in the blood, from .62 to .7 per cent. The specific gravity does not usually exceed 1010. Epstein has made some interesting studies upon these edema fluids. He states that these fluids are unlike those present in any other condition and are composed almost exclusively of inorganic and nitrogenous salts and water, but that they differ somewhat according to whether they are cutaneous, pleural or abdominal effusions. The cutaneous effusions are characterized by a very low protein content, a small amount of noncoagulable nitrogen, a relatively very large quantity of globulin, and the chlorids in about the same proportion as in the blood-serum. The pleural effusions differ from the cutaneous by their higher protein content. In them, the incoagulable nitrogen is uniformly low, and the chlorids vary in amount according to the case. The abdominal fluids in general are less rich in protein than pleural effusions.

There has been and still is much discussion as to the cause of edema occurring in kidney diseases. On the experimental side, it has pretty generally been found that there must be three factors present for the production of edema, *viz.*, glomerular lesion, vascular lesion, and hydreemia (Pearce). According to Widal the edema is a result of a failure on the part of the kidney to excrete salt and water. Fischer believes that the cause of edema is to be found in the tissue, and that it is due to an increased affinity of the colloids of the tissues for water and this in turn is due to the accumulation of acids in the tissues. Volhard and Fahr state that the cause of the edema is to be sought in a pathologically increased permeability of the blood-vessels, and this apparently arises under the influence of substances which originate from the degeneration of the kidney epithelium and is carried into the circulation. They state further that in the stage of most marked edema there is no hydreemia, and that the viscosity of the blood may be increased, which they think shows that the edema does not depend upon a water retention, the result of insufficient excretion of water, but on the contrary that the poor water excretion is apparently the result of a lack of water in the blood.

Epstein, as a result of a study of the blood-serum and edema fluids in these cases, offers a similar view. He states that the loss of protein incurred by the blood-serum through the continuous albuminuria causes a decrease in the osmotic pressure of the blood. Through this condition, and the additional circumstance that large quantities of fats and lipoids accumulate therein, the physicochemical state of the blood is disturbed to such an extent that it loses much of the power which it normally possesses to withdraw fluids from the tissues; consequently deposition of fluid in the tissues occurs. In other words, the edema in this type of nephritis is not necessarily the result of lessened permeability or functional powers of the kidneys to eliminate salt and water, but is the result of a change in the character of the blood.

In the chest there will frequently be found the physical signs of fluid in both pleural cavities. The heart does not show any evidence of hypertrophy which with the normal blood-pressure forms one of the chief characteristics of the disease. In the abdomen may be found the signs of the presence of free fluid.

Blood.—Unless anemia is present as a result of the causative disease, the red blood-cells are not diminished. A case dependent upon syphilis showed red blood-cells 5,182,000, leukocytes 9000, polymorphonuclears 66 per cent., small lymphocytes 31 per cent., large mononuclears 0, eosinophils 3 per cent., Wassermann positive. There are conflicting views with respect to hydremia. Volhard and Fahr state that there is no hydremia at the time of most marked edema, that on the contrary the blood is abnormally concentrated. They state further that the term hydremia is confusing, that the assumption of an actual blood thinning is only justifiable when the number of red blood-cells is diminished in the thin suspension, that one is not justified in concluding that a hydremia is present from the decrease in the protein content. This, however, is not in accord with the usual views as to hydremia. Hewlett states that hydremia means a watery condition of the blood, and that since the corpuscular elements of the blood are relatively rich in solids, their number markedly influences the percentage of water in the total blood. He states, however, that it seems advisable to exclude from consideration the changes of the blood concentration which are caused by variation in the number of corpuscles, and thus restricted, the term hydremia means a watery condition of the blood-serum or blood-plasma. Epstein's examination in two cases of nephrosis shows the following:

Per 100 c.c.

Total Protein (Gram)	Incoagulable Nitrogen (Gram)	Globulin (Gram)	Chlorid (Gram)	Cholesterol (Gram)	Globulin in Protein (Per Cent.)
3.611	0.063	2.038	0.404	0.760	59
2.731	0.101	2.598	0.390	1.226	95

Urine.—The quantity of urine in the stage of the formation and maintenance of edema is markedly diminished. Less than 500 c.c.

in twenty-four hours is not infrequent. During the stage of elimination of edema the quantity is increased. It varies in color from a grayish yellow to a dark brown and shows a heavy precipitate of urates. With oliguria the specific gravity is high, varying from 1025 to 1050. With the increase of quantity it may be very low. The reaction is usually acid, but on account of the ease with which decomposition occurs it may be found to be alkaline. The albumin content is high, which with the absence of macroscopical blood forms the chief characteristics of the urine in this condition. The microscopical examination of the sediment gives variable results. There may be numerous casts of all kinds, fatty epithelium and leukocytes. This is especially the case in the edematous stage. Later, casts, fatty epithelium, and leukocytes may be scant. Munk has emphasized the presence of double refracting substances as of importance in the diagnosis of nephrosis.

FUNCTIONAL TESTS.—As a rule, it may be stated that the usual tests for the determination of kidney function show good results. Volhard and Fahr state that the water test, in which 1500 c.c. of water are taken on an empty stomach, may be poor in the stage of marked edema and oliguria, but that this is due to the increased permeability of the vessels rather than to kidney insufficiency. The same obtains with reference to the salt excretion. On the contrary, the nitrogen output in the urine is increased due to the increased nitrogen concentration. According to these authors the methods of Schlayer have given paradoxical results. In one case the author has obtained the following results:

MOSENTHAL TEST-MEAL

Time of Day	Quantity	Specific Gravity	NaCl		Nitrogen	
			Per Cent.	Grams	Per Cent.	Grams
8 A. M.—10 A. M.	70 c.c.	1020				
10 A. M.—12 M.	60 c.c.	1020				
12 M. — 2 P. M.	62 c.c.	1018				
2 — 4 P. M.	72 c.c.	1020				
4 — 6 P. M.	87 c.c.	1020				
6 — 8 P. M.	74 c.c.	1020				
Total Day	425 c.c.		.1	.425	1.5	6.37
Night (8 P. M.—8 A. M.)	600 c.c.		.04	.24	1.	6.00
Total 24 hrs.	1025 c.c.			.665		12.37
Fluid intake	1760 c.c.			8.5		13.4
Difference	+ 735 c.c.			— 7.835		1.03

Weight	Period	Blood Urea per 100 c.c.	Urine				Ambard's Coefficient
			Period	24 hrs.	Urea	Urea	
57 kg.	4-6 P. M.	40 mg.	87 c.c.	1044 c.c.	18.5 c.c. (in 24 hrs.)	17.7 c.c. (in liter)	.093

The intravenous injection of 1 c.c. phenolsulphonephthalein showed an excretion of 55 per cent. in two hours. The alkali reserve of the blood by Marriott's method was 8.5. In another case the total non-protein nitrogen was 38 mg. per 100 c.c. of blood.

UREMIA.—True uremia with kidney insufficiency is rarely if ever present. Volhard and Fahr state that eclamptic uremia may occur. However, the occurrence of convulsions should arouse the suspicion of cerebral complications of the causative disease, *e.g.*, lues, tuberculosis or brain tumor.

Diagnosis.—The diagnosis of nephrosis is made upon the presence of edema, the absence of increased blood-pressure, the urinary findings and well-maintained kidney function. Chronic glomerulonephritis in the second state with good kidney function is differentiated by the increased blood-pressure; the hemorrhagic focal nephritides by the absence of marked edema and the presence of hematuria. Certain complications, *e.g.*, the occurrence of nephrosis in an old arteriosclerotic, may render the diagnosis uncertain.

Complications.—The anatomical examination often shows that amyloid degeneration is present in cases of nephrosis of known etiology, *e.g.*, those cases dependent upon tuberculosis, syphilis, tumor cachexia and chronic suppurations. It has been held that certain clinical findings such as the absence of increased blood-pressure, a tendency to diarrhea, an abundant urine with little sediment, low specific gravity and a large quantity of albumin are characteristic of the amyloid kidney. But Volhard and Fahr emphasize the fact that all of these symptoms are found in nephrosis without amyloid degeneration, and that the amyloid degeneration is to be regarded only as a complication, which often cannot be diagnosed clinically. Bronchitis and pneumonia are not infrequent complications of nephrosis as is also the occurrence of infectious peritonitis. In 4 of Volhard and Fahr's cases, a pneumococcic peritonitis developing from bronchitis and pneumonia occurred. One of the author's cases was complicated with pneumonia and another by an infectious peritonitis.

Clinical Varieties.—The course of nephrosis is dependent largely upon the etiology. Those cases dependent upon pregnancy, recent lues, and diphtheria may show a relatively acute course, while those depending upon tuberculosis, chronic suppurative processes, old lues, and genuine nephrosis, *i.e.*, those cases without known etiology, pursue a distinctly chronic course. These latter may be separated into three stages with more or less distinct clinical and anatomical manifestations,—the first stage or that of hydrops corresponding to granular and fatty degeneration of the epithelium of the kidney tubules; the second or edema-free stage corresponding to the anatomical stage showing secondary inflammatory reaction in the interstitial tissue; the third or end stage corresponding to the nephrotic contracted kidney.

After a variable period of time, depending upon different conditions—etiology, severity, and treatment—the edema of the first stage disappears, or the effusions into the serious cavities only may remain. The

subjective symptoms of the patients in the second stage are few and the condition is recognized as nephrosis by the absence of increased blood-pressure and the urine with high specific gravity and excessive albuminuria. Less frequently this stage terminates in the third stage, characterized by absence of increased blood-pressure and cardiac hypertrophy with kidney insufficiency. These patients may show as poor results to the water and concentration tests as the patients with glomerulonephritis with kidney insufficiency. However, the ability to dilute is maintained in contradistinction to the nephritic kidney, and non-protein nitrogen is rarely present in excessive amount in the blood in the end stage of nephrosis.

Treatment.—The rational prophylaxis of any disease consists in the institution of measures to prevent those conditions or diseases which are known to stand in etiological relation to it. So the **prophylaxis** of nephrosis of known etiology concerns itself with the measures for the prevention of tuberculosis, diphtheria, syphilis, chronic suppurations, measles, and possibly other infectious diseases or at least with especial protection of the kidneys in these diseases as well as in certain endogenous intoxications as pregnancy and the cachectic conditions occurring in malignant tumors. The nephrosis without known cause is designated "genuine" in contradistinction to those of known etiology. It is possible that exposure to wet and cold, hereditary predisposition, and continued high protein diet may have some influence in the production of genuine nephrosis, so that the individual whose family history might show a predisposition to the condition should be advised to avoid undue exposure to wet and cold as well as to be impressed with the possible serious consequences of indulgence in a high protein diet.

The treatment of the disease after it has developed also consists in the treatment of the causative disease when it is possible to discover this. Active syphilis, as shown by a positive Wassermann, should especially receive appropriate treatment. The chief symptom which calls for treatment is the general anasarca. Conflicting methods are advocated by different authors according to the view which they may happen to hold with respect to the cause of the edema.

Fischer claims that acids increase, and sodium chlorid in concentrated solution decreases, the hydrophilic properties of colloids. He would therefore give **sodium carbonate** in a concentrated solution of **sodium chlorid**. This is administered in the following formula: sodium carbonate crystallized, 10 grams (154.32 grains), or dried carbonate, 3.7 grams (57.103 grains), sodium chlorid, 14 grams (216.059 grains), water 1000 c.c. by proctoclysis, or the sodium carbonate and sodium chlorid may be administered slowly intravenously. The solution for intravenous injection is prepared in the following way: Dissolve 10 grams of crystallized sodium carbonate or 3.7 grams of the dried carbonate in a little distilled and sterilized water; the sodium chlorid is then dissolved in an appropriate amount of distilled water and sterilized by heat; after this solution has cooled sufficiently, the carbonate solution is added to it. Fischer claims that this procedure drives the

water out of the tissues into the serous cavities from which it must be removed by paracentesis. In a few cases of nephrosis, the author has not found evidence of acidosis in the carbon dioxid tension of the alveolar air and the alkali reserve of the blood. Rowntree and Christian have seen the edema unquestionably increased by the application of this treatment.

Epstein, believing that conditions of nutritional disturbance are present and that the edema is associated with definite changes in the blood, suggests the following treatment:

"In the less severe cases the patients are put on a **high protein diet** (from 80 to 200 grams of proteins daily) with a **small quantity of carbohydrates** and a **total restriction of fats**. The total food value of the diet ranges between 1200 and 2400 calories. In very severe cases repeated **transfusions of blood** are resorted to simultaneously with the administration of a high-protein, fat-poor diet. At each transfusion (about 500 c.c.) an equal amount of the patient's blood is first removed. The effect of this procedure is threefold: (a) It ameliorates the anemia; (b) it increases the protein content of the blood; and (c) it diminishes the fat content of the serum. As is to be expected, the effects of transfusion are temporary, but they serve to initiate the desired changes in the composition of the blood-serum. The chief reliance is placed on a high protein diet. The chlorides and water are only moderately restricted."

He states that the results of this treatment carried out in 8 cases appear encouraging. Epstein further states that we possess no evidence that protein diet *per se* is deleterious to the kidneys. The later experimental work of Newburgh referred to above should be considered in this connection.

According to the author's own experience, these patients should be kept at absolute **rest in bed** until the edema subsides. The bedding and clothing should be warm to promote the action of the skin. Since there is no impairment of the kidney function as expressed by a decreased phthalein output nor any increase in the blood urea there is no indication for an especially low protein diet. Whether the salt and water retention is due to insufficiency of the kidneys for these substances, or is due to the condition of the blood and tissues, may be discussed, but the fact remains that salt and water are retained and indicate a salt-poor, water-poor diet. As a rule the institution of this diet is followed by a marked subsidence of the edema from the subcutaneous tissues as well as from the serous cavities. Where there is difficulty in getting such a diet prepared, the author has found that the **Karell diet** (200 c.c. of milk four times a day and nothing else) is followed by good results. If the edema is extreme, other dehydrating measures may be employed. In the absence of diarrhea which, however, is frequently present, **compound jalap powder**, 1 dram (3.9 grams) may be given once daily. **Sweating by the hot air bath or wet pack** will, however, usually give better results. No beneficial results have been obtained from diuretics. The author has not found multiple incisions

nor the insertion of Southey's tube necessary nor does he think they are desirable. If the accumulation of fluid in the serous cavities is so great as to interfere with the comfort of the patient, **paracentesis** should be performed and repeated as often as necessary. Due attention should be paid to the occurrence of complications such as bronchitis and pneumonia and the treatment appropriate for these conditions instituted. The occurrence of infectious peritonitis, which not infrequently develops, demands surgical interference. Careful attention should be given the patient during convalescence, his salt and water tolerance carefully determined, exposure to undue cold and wet should be avoided, and the patient urged to pay due regard to the occurrence of focal infections, for the recurrence of the symptoms of nephrosis are extremely likely to recur.

Prognosis.—The prognosis is good so far as death referable to the kidney condition is concerned. In none of Volhard and Fahr's 55 cases has death resulted from the kidney lesion, nor in the 10 cases studied by the author. The recovery from the kidney condition is dependent largely upon the causative disease. Those cases dependent upon tuberculosis and chronic suppurative diseases rarely recover, while those due to pregnancy, diphtheria and lues frequently do. The occurrence of complications also affect the prognosis. Bronchitis and pneumonia affect it seriously. One of the author's patients with pneumonia, however, completely recovered. Infectious peritonitis is almost always fatal. Cases of genuine nephrosis may eventually recover after a very prolonged course.

Pathology.—Fahr divides the nephroses pathologically into three groups, viz., simple nephrosis, specially characterized nephrosis, represented by the sublimate kidney, and complicated nephrosis, represented by the amyloid kidney.

The simple nephrosis, he further subdivides into four stages histologically, viz.:

First Stage.—Cloudy swelling.

Second Stage.—Histologically demonstrable degenerative lesions in the epithelium.

Third Stage.—Secondary inflammatory reaction in the interstitial tissue.

Fourth Stage.—The contraction stage.

FIRST STAGE OR STAGE OF CLOUDY SWELLING.—*Macroscopical.*—The kidney is usually slightly larger than normal; the capsule strips easily, the outer surface is smooth, varying from brown to yellow in color; it is edematous; on cut surface it is of a brownish to a yellow opaque color; the surface markings are obscured.

Microscopical.—The epithelium of the proximal convoluted tubules is swollen, narrowing the lumen of the tubules. Altmann's granules are enlarged and in some areas regularly arranged and in other areas irregularly arranged. The nuclei are generally well preserved. Fatty changes may occur in the cells of Henle's loops. The epithelium of the ascending loop of Henle and the distal convoluted tubules generally

are not affected; if so, not to the extent of the proximal convoluted tubules. There is exudation of albumin into Bowman's capsule and in the lumen of the tubules. The glomerular loops are well filled with blood. These changes which are quite frequent in all infectious processes usually completely recover, but may pass over into the next or second stage.

SECOND STAGE.—*Macroscopical.*—The kidney is enlarged; the capsule strips easily; the outer surface is smooth; the consistence is spongy; the cortex is widened and of a smutty color; the medulla is brown in color in marked contrast to the cortex.

Microscopical.—The chief characteristics of this stage are hyalin, granular and fatty degeneration of the epithelium of the proximal convoluted tubules. The nuclei of these cells are partly preserved and partly destroyed. There has been much discussion as to the origin and significance of these hyalin granules. Some maintain that they arise from the Altmann granules and signify a hyperfunction. The weight of opinion seems to regard these cells as the result of a degenerative process. The distal portion of the proximal convoluted tubule, which frequently has been confused with the ascending limb of Henle's loop, is chiefly affected. Fatty degeneration is also present usually in a greater degree than in the stage of cloudy swelling. This usually increases with the degree of hyalin degeneration, but the changes are not exactly parallel. The fatty changes attack chiefly the proximal convoluted tubules, though the ascending limb of Henle's loop and the distal convoluted tubule may be involved to a less extent. Occasionally casts are present in the descending limb and loop.

In the capsular space there is coagulated albumin and occasionally desquamated epithelium. The glomerular loops are well filled with blood, but there are no signs of inflammation. The capillaries of the medulla are also well filled, though there is no evidence of inflammatory reaction in the interstitial tissue. This stage also usually heals, but rarely passes over into the third stage.

THIRD STAGE.—*Macroscopical.*—The macroscopical appearance is more characteristic in this stage than in the two previous stages. The kidney is smaller than that of the second stage, but usually larger than normal. The capsule strips easily. The outer surface is smooth and smutty in appearance. There are opaque grayish spots distributed throughout the substance and the consistence is soft and doughy. On cut surface the cortex is widened in appearance similar to the outer surface, with gray spots and streaks. The markings are obscured. The medulla is brownish in color.

Microscopical.—The microscopical appearance varies somewhat according to the age of the process. The proximal convoluted tubules are widened. The epithelium presents a honey-comb appearance, some of the nuclei being well preserved, others destroyed. Hyalin granular degeneration is apparently less than in the second stage, though fatty degeneration is more marked. The fat is single refracting. The degenerative changes are not so marked in the ascending limb of Henle and

the distal convoluted tubules and the honey-comb appearance of the epithelium is here absent. There are a few casts which sometimes take the fat strain in the collecting tubules. The glomerular loops are well filled and the epithelium may here show some fatty change. There is some lymphocytic infiltration in the interstitial tissue though there are no very large areas. The older stages of the process differ from the above in that double refracting substance may be present in the glomeruli and there is marked lymphocytic infiltration in the interstitial tissue with the formation of granulation tissue. In large areas the tubules may be destroyed though the glomeruli in these areas are fairly well preserved, but some show concentric pericapsular thickening. This stage rarely passes over into the fourth stage. Volhard and Fahr have observed only one case of the fourth stage.

FOURTH STAGE.—*Macroscopical.*—The kidneys are much diminished in size; the capsule is adherent; the outer surface is irregular, granular areas of a yellowish color alternating with smooth areas of a dark gray, glassy appearance; the consistency is firm; on cut section the cortex and medulla coalesce; there are dark brown streaks throughout and the markings are obscured.

Microscopical.—The tubules appear as islands surrounded by connective tissue. They are wrinkled and show desquamation and evidence of regeneration of epithelium. Granular and fatty degeneration are less in evidence than in the previous stages. The glomeruli are degenerated by concentric capsular thickening. In some areas there may be increase of capsular cells but generally distinct evidence of inflammation is absent. The heart in this case was not hypertrophied but showed brown atrophy.

The Amyloid Kidney

Formerly there was a tendency to regard the amyloid kidney as a distinct disease both clinically and pathologically. But lately, it is more and more considered an incident in the course of various nephropathies. McCallum states, "In general, then, while some of the symptoms of nephritis are changed by the amyloid in the kidney, we may regard its presence there as incidental, rather than as a cause of nephritis or as constituting a new form of disease." We have seen that the same symptoms are present in nephrosis with and without amyloid. Fahr regards the amyloid kidney pathologically as complicated nephrosis. The same author divides his material of amyloid kidneys into three groups, which he designates as the first, second, and third stages corresponding respectively to the second, third, and fourth stages of nephrosis.

In the first stage, the gross appearance of the kidney is very similar to that of the second stage of nephrosis, though on cut surface it is drier and more opaque. There is a marked difference in the consistency which is decidedly stiff. Only very occasionally is the lardaceous, glassy appearance of the second stage present.

On microscopical examination, granular degeneration is prominent in the proximal convoluted tubules, and fatty changes are about the same as in the second stage of nephrosis. Amyloid is deposited beneath the endothelial layer of the glomerular loops, which are, however, well filled with blood and are permeable. The glomerular epithelium may contain fine particles of fat. The vessels are intact except for the deposits of amyloid. In the interstitial tissue may be seen occasional leukocytes and beginning inflammatory reaction.

The second stage, which corresponds to the third stage of nephrosis, is most frequently encountered, and macroscopically the differences from that of the third stage of nephrosis are quite marked. The kidney is decidedly enlarged, sometimes two or three times the size of the normal kidney. On cut surface the contrast in color between the cortex and medulla may be even more distinct than in simple nephrosis of the corresponding stage. The cortex presents a smuttier gray color.

Microscopically, epithelial desquamation in the tubules is greater, though here the condition with respect to fatty degeneration is about the same. Granular degeneration is more marked and casts are more numerous, especially in the primary collecting tubules. Double refracting lipoids are present in the interstitial tissue as well as in the epithelium. The tubules are widened and lined with very flat epithelial cells. The proximal convoluted tubules are chiefly affected by the degenerative processes.

The glomeruli and capillaries show more marked deposits of amyloid than the previous stage; still many of the glomerular loops are free of amyloid and are well filled with blood. The large blood-vessels are intact and the interstitial tissue shows about the same condition as the third stage of nephrosis.

In the third stage of amyloid kidney, the differences from the fourth stage of nephrosis are still more considerable both macroscopically and microscopically. The kidney is normal or slightly diminished in size. The outer surface is usually smooth, although occasionally slight granulations may be seen. The color is more flecked with brown. On cut section, the cortex and medulla are well contrasted and the markings of the cortex are obscured. The consistency is of marked stiffness and distinctly firmer than in the second stage. The opaque areas on cut surface have a more glassy appearance.

On microscopical examination, the connective tissue increase is diffuse, not focal as in the last stage of nephrosis. The tubules do not appear as islands surrounded by connective tissue, which explains the absence of granules on the surface. The tubules are widened and there are focal areas of small round cell infiltration. In the parenchyma there are areas of degeneration extending in streaks around which there is infiltration of small round cells. While the preserved tubules lie close together here, outspoken island formation, as in chronic nephrosis and in the secondary contracted kidney, is not observed. The initial collecting tubules are wider than in the preceding stage and filled with casts. There is granular degeneration of the epithelium of the proximal con-

voluted tubules, and conditions with respect to fatty changes are about the same as in the previous stage. The presence of double refracting lipoids is not prominent. The glomeruli are large, filling out the capsule, and show large shadows of amyloid; still some of the glomerular loops are always permeable and well filled with blood. In young individuals the blood-vessels, with the exception of the presence of amyloid, are intact. In old individuals, however, the amyloid is deposited in kidneys, the vessels of which are already affected with arteriosclerosis. Indeed, not infrequently, the amyloid occurs in arteriosclerotically contracted kidneys. Fahr describes two cases, in one of which especially the presence of glomerulonephritis might be considered, but the author concludes that the evidence of glomerulonephritis is not sufficient to classify these cases with those of outspoken glomerulonephritis. Ophuls, however, reports amyloid in secondary contracted kidneys—advanced glomerulonephritis—but in these kidneys there is also present chronic parenchymatous nephritis—the nephrosis of Fahr.

The amyloid kidney, unless occurring in an already arteriosclerotic kidney, is not accompanied by increased blood-pressure and cardiac hypertrophy.

Necrotizing Nephrosis

(Bichlorid Kidney)

Symptomatology.—CLINICAL HISTORY.—In poisoning by mercury, one would expect degeneration of the epithelium of the kidney tubules in its purest form, and it might be surprising how the clinical manifestations in these cases differ from those described above as characteristic for nephrosis. In the bichlorid kidney there is not marked edema, there is frequently anuria, the kidney function is often markedly impaired—high non-protein nitrogen in the blood, low phenolsulphonaphthalein excretion, manifestations of uremia, and finally slightly increased blood-pressure. The clinical manifestations, laboratory findings, etc., may be illustrated in the following actual incidence:

CASE HISTORY.—Mrs. ———, thirty years of age; housewife.

Anamnesis.—Family history negative. No serious illness in past history. Two children. Domestic infelicity. At about 8 P. M., May 31, 1916, patient swallowed 52.5 grains (3.4324 grams)—seven 7.5 grain tablets—bichlorid of mercury dissolved in a glassful of water. The patient vomited and complained of pain and burning under the sternum. Her physician was called immediately. He reached the patient in about fifteen minutes. The stomach was washed out thoroughly with milk. Vomiting continued at intervals through the night and there were mucosanguinolent discharges from the bowels. Urine was voided during the night, the last time just before day. The patient was admitted to the hospital at 5 P. M., June 1, 1916.

Status Præsens.—A well-developed, highly cultivated lady, in a good state of nutrition; very weak, but anxious to recover. The mucous

membranes of the mouth and throat were very red. She complained of soreness of throat, difficulty in swallowing, burning under the sternum and griping pains in the abdomen. There were frequent discharges from the bowels—mucus and blood—with tenesmus. The temperature was 100.4° F. (38° C.) and pulse 110.

For nine days there was great weakness, depression, much nausea and vomiting, frequent bowel movements—six to twenty-seven daily—backache, headache, twitching of the muscles, delirium and hiccup. On June 8 there was very severe hemorrhage from the stomach and bowels. There were severe salivation and stomatitis. During this time there was no edema; later slight puffiness of the face developed.

Urine.—There was complete anuria from June 1 to June 9. On the latter date, about 150 c.c. were voided. It was of a pale greenish tinge, specific gravity 1012, faintly acid in reaction; there was a trace of albumin; the centrifuged specimen contained a few red blood-cells, leukocytes, many degenerated epithelial cells, broad and narrow finely granular and epithelial casts. It rapidly increased in amount as follows: June 10, 450 c.c.; June 11, 1190 c.c.; June 12, 1395 c.c.; June 13, 1500 c.c.; June 14, 2580 c.c.; June 15, 2250 c.c.; June 16, 1650 c.c., and continued at about this quantity for the twenty-four hours until discharge. On June 16 the phenolsulphonephthalein excretion in two hours was 20 per cent.

Blood.—On June 3—three days from onset—the total non-protein nitrogen was 101 mg. per 100 c.c.; June 8, Hgb. 30 per cent. (Tallqvist); June 21, Hgb. 35 per cent. (Tallqvist); erythrocytes, 1,584,000; leukocytes, 12,600; polymorphonuclears, 82 per cent.; small lymphocytes, 19 per cent.; large mononuclears, 9 per cent.; and eosinophils 0.

Blood-pressure.—On June 2, the systolic blood-pressure was 135, diastolic 80; June 8, systolic 140, diastolic 80 (before the severe hemorrhages); and on June 10, systolic 120, diastolic 55. The patient was discharged from the hospital July 7, 1916. At that time the urine showed specific gravity 1021, no albumin, no casts. Her recovery has been complete. She has since given birth to a baby without any ill effects.

In marked contrast to nephrosis, edema is rarely observed in the mercury kidney. However, Volhard and Fahr report a case in which the edema was a marked feature in a child, the result of calomel medication, and cite a case of Ascoli where the edema was also marked; in this case the poisoning resulted from breathing the air of a room in which bichlorid had been freely used for disinfection purposes. They suggest that these cases may serve to bridge over the gaps from the mild cases to those severe cases in which necrosis of the kidney epithelium is rapidly produced. This view may also be supported by a study of the urine in difficult cases. In mild cases, polyuria without following oliguria or anuria may occur. In severe cases the oliguria may result with high degree of albuminuria as in nephrosis. While in still severer cases an oliguria may precede the anuria which may continue until death or be succeeded by an hyposthenuria. In the period preceding and

following the anuria, the urine is of low specific gravity with low nitrogen and sodium chlorid concentration.

The condition of the blood-pressure also varies. In the cases with anuria and azotemia it is usually high and is probably due to the increased nitrogen retention in the blood.

It is often difficult to tell whether certain symptoms, as the gastro-intestinal symptoms, great asthenia, muscular twitching, stupor, etc., are to be referred to the uremia or to the poisonous effects of the mercury. Convulsions and psychoses rarely occur, though Foster has reported the occurrence of these in one case.

Treatment.—It is questionable whether milk has any antidotal effect. Also it should not be forgotten that mercury is soluble in excess of **egg albumen**. Fantus suggests **sodium phosphate** and **sodium acetate** as antidotes. If sodium phosphate cannot be obtained, he substitutes the following solution: **sodium hypophosphite**, 1 gram (15.43 grams), water 10 c.c., **hydrogen peroxid** solution, 5 c.c.

The antidote should be administered at once—the white of one egg to each 4 grains (.26 gram) of mercury, or the hypophosphite in ten times the amount of mercury. The stomach should be thoroughly washed out; it may be repeated if deemed necessary.

If anuria sets in, it will be desirable to **flush** out, if possible, the kidney tubules. For this purpose 500 c.c. of **Fischer's solution** may be administered intravenously. (For preparation of solution see treatment of Nephrosis.)

This should be supplemented as suggested by Lambert and King by continuous **proctoclysis** of 1 dram (3.9 grams) sodium acetate to the pint of water. To facilitate the removal of the poison eliminated by the stomach and intestinal tract, **gastric lavage** and **high colonic irrigation with plain water** may be resorted to twice daily. As demulcent drinks **starch water**, **slippery elm** or **flax seed tea** may be given at frequent intervals. The duration of this treatment will depend upon the rapidity with which the mercury is eliminated. It should be continued as long as mercury can be detected in the urine and intestinal discharges. For this the **method of Vögel** may be used. This consists in the separation of the mercury from its albuminous combination with organic material by treating it with pure hydrochloric acid and subliming it in a sealed tube to form an amalgam on gold or copper foil.

The nutrition of the patient may be sustained by giving the juice of one lemon, two-thirds of a cup of water and six tablespoonfuls of milk-sugar four times a day. This may be alternated with a glass of sweet milk.

If severe hemorrhage occur, the subcutaneous injection of **horse serum**, 20 c.c., or **coagulose** will be indicated. The horse serum seemed to have a very good effect in the case here reported.

Prognosis.—The prognosis as to life will depend largely upon how long before anuria sets in and how long it continues. Usually the earlier it occurs after poisoning the graver the prognosis. Still in the case reported anuria set in about six hours and continued for eight days.

In the milder cases followed by polyuria or in the more severe cases with characteristic nephrotic urine, recovery is the rule. The prognosis is more doubtful in those followed by a long-continued hyposthenuria. It is often doubtful as to whether death should be attributed directly to the mercury poisoning or to the urinary poisoning—true uremia. Death may result from severe hemorrhage consequent upon the separation of slough in the gastro-intestinal tract.

Pathology.—Heineke and others have shown that the kidneys show characteristic changes in bichlorid of mercury poisoning.

MACROSCOPICAL.—The size of the kidneys varies somewhat according to the duration of the poisoning. In the early stage before inflammatory reaction has taken place in the interstitial tissue, they are of average size, later they are somewhat swollen. The capsule strips easily; the outer surface is smooth, the cortex is broad, sometimes welling out of the capsule. On cut surface, the cortex is broadened and of a yellowish color in marked contrast to the dark brown color of the pyramids. The cortical markings are obscure.

MICROSCOPICAL.—Instead of cloudy swelling, hyalin granular and fatty degeneration of the epithelium of the proximal convoluted tubules, there is necrosis with evidences of regeneration of the epithelium. There is also a tendency to the deposition of calcium in the epithelium. This possibly is greater in those cases with less severe necrosis. These latter cases are more likely to be associated with evidence of inflammatory reaction in the interstitial tissue. The glomeruli do not usually show any evidence of inflammatory changes.

GLOMERULONEPHRITIDES

Etiology.—The present state of knowledge with respect to the etiology of nephritis does not permit a classification on an etiological basis, however desirable this may be. We have seen that the same etiologic factor may at one time produce a nephrosis and at another time a nephritis. In the nephritides we are met by the same unexplainable fact. Scarlet fever may be followed by a diffuse glomerulonephritis or a focal nephritis, nor is there any difference in the clinical history and pathologic anatomy of a diffuse or focal nephritis resulting from a streptococcic infection and a diffuse or focal nephritis in a pneumococcic infection. The cause for each group of nephritis as well as for the subdivisions of each group is so uniform that the etiology for all forms may be considered together.

The idea of a bacterial origin of nephritis is rapidly gaining ground. There is scarcely an infectious disease in which at one time or another a nephritis has not been observed. Yet those diseases especially associated with streptococci and less often with pneumococci have been especially connected with nephritis. Thus, Aschoff mentions as etiologic factors, scarlet fever, anginas, rheumatic fever, pneumonia and other infections with the streptococcus vulgaris. Bacteria have been found in

the urine of nephritic patients and it is claimed these bacteria are capable of producing the changes in the urine and in the kidney of nephritis. Volhard and Fahr state that the most important facts with respect to the etiology of nephritis may be summarized in two sentences, as follows:

“(1) The pathogenic cause of every nephritis is almost without exception a bacterial infection.

“(2) The different forms and stages of nephritis have the same etiology.”

The nephritis in association with malaria, which is estimated to occur in from 2 to 5 per cent. of estivo-autumnal infections, is probably an exception in which a protozoal infection may be an etiologic factor. Other exceptions are pregnancy, the relation of which to nephritis is not thoroughly explained, and possibly also lead, though this stands in more definite relation etiologically to the sclerosis.

While the greater rôle is assigned to streptococci and a lesser one to pneumococci in the causation of nephritis, the pathogenesis is obscure. The diffuse glomerulonephritides have usually been attributed to the endotoxins of the streptococci circulating in the blood, which thus conveyed to the kidney for excretion produce injury in the glomeruli which excite an inflammatory reaction. Ophüls, however, points out difficulties in the acceptance of this theory. It is, according to this author, difficult to understand how the poisons could ever become so concentrated in the blood that they would produce the intensely inflammatory conditions in the kidney and in no other organs, or the fact that all glomeruli are not affected similarly and simultaneously. Löhlein postulated the embolic origin of focal glomerulonephritis occurring in infectious endocarditis, although he was unable to demonstrate the presence of streptococci in the glomeruli of his material which represented a late stage of the disease. In early cases Fahr and Baehr were able to demonstrate their presence, proving the deduction of Löhlein. Ophüls extends this idea to the pathogenesis of diffuse glomerulonephritis, basing his view on the presence of hyalin masses to be found in the glomeruli of most all cases during the acute stages of the disease. Ophüls regards these masses as the result of thrombosis and subsequent necrosis of the capillary wall which precede the other changes in the glomeruli. He as others, however, has not been able to demonstrate the presence of bacteria in such glomeruli. This, however, according to Ophüls, may be the result of the rapid destruction of the bacteria by the strong bacteriolytic property acquired by the endothelium of the glomeruli in cases of chronic septicemia. It has been observed clinically that the diffuse glomerulonephritides supposedly of toxic origin as a rule develop two or three weeks after the occurrence of the causative disease, as in scarlet fever and angina, while the focal glomerulonephritides, supposedly of infectious origin, develop along with the causative infection.

Another important problem connected with the etiology of nephritis awaiting satisfactory explanation is the evolution of the disease—the

progress of the disease from the acute to the chronic stages. That such a progression occurs is attested by the presence of an unbroken series in many cases. The time in which and the extent to which the chronic stages will develop is dependent chiefly upon the intensity of the acute stage and resulting upon this how much functional tissue is left. Yet the question arises as to how the various stages in the process are brought about. Does the primary toxin or infectious agent continue to act until more and more of the functional portions of the kidney is destroyed? The decided tendency of the acute nephritis to heal is against this view. Is the progress due to the fact that with the destruction of much of the functional portion of the kidney, the compensatory power of the preserved portion fails, resulting in more marked azotemia with formation of toxic substances which act as inflammatory irritants? The occurrence of albuminuric retinitis and the inflammation of serous membranes late in the disease would tend to support this, although this does not seem to offer an adequate explanation. Finally are the end results due to repeated insults to the kidney, as seems to be the case in some cases of so-called chronic endocarditis, chronic arthritis, chronic anemias, and the like? All of these questions await a satisfactory answer.

The following table from Volhard and Fahr show some of the important etiologic relations of the infectious diseases to the two groups of nephritis and their various subdivisions:

SYNOPSIS OF THE ETIOLOGY OF THE NEPHRITIDES

	A. Diffuse Nephritis			B. Focal Nephritis				Total
	Acute Stage	Chronic Stage	End Stage	(a) Glomerular		(b) Interstitial	(c) Embolic	
				Acute	Chronic			
Angina	17	7	13	11	4	1		53
Scarlet Fever.....	10	2		6	4	4		26
Infected Wounds..	7	3	1	2	2	2	2	19
Erysipelas	1		1	3				5
Rheumatic Fever and Endocarditis	2	1	2	1			5	11
Purpura				1				3
Cold, Influenza- like Diseases....								23
Otitis, Rhinitis....	8	5	6	1	3			
Pneumonia								
Bronchitis								
Empyema								13
Pleuritis	6		1	3		3		6
Tuberculosis	3	1		1	1			
Gastro-enteritis ...								3
Weil's Disease....		1		2				1
Malaria		1						3
Lead Poisoning...			3					7
Pregnancy	4	2	1					25
Unknown	2	9	10	1	2		1	
Total	62	32	38	32	16	10	8	198

From this table is seen the marked prominence of bacterial infections in etiology of nephritis in 161 of 179 cases in which the cause was known. The great importance of streptococci in particular is shown by the frequency with which these diseases such as tonsillitis, scarlet fever, infected wounds, erysipelas, rheumatic fever and endocarditis, purpura, sinus infections and otitis media, in which streptococci are present, occur in connection with nephritis. Angina occurs as the primary disease in one-fourth of all cases. When it is considered that the tonsils and the pharyngeal lymphatic ring are the portals of entry in the diseases here referred to streptococci, it is seen that these structures are primarily infected in about three-fourths of the cases of known cause—147 in 179 cases. Infected wounds are apparently the cause in 17 cases. The illustrative case reported in connection with acute diffuse glomerulonephritis is clearly due to a streptococcic infection of the hand. From the table erysipelas would seem to be a less frequent cause of nephritis. The author recalls a case in which acute diffuse glomerulonephritis developed in the course of facial erysipelas. The case gradually progressed to the end stage of diffuse glomerulonephritis and death resulted from uremia in about five years after the onset of the acute nephritis. Pneumococcic infections are also infrequent, though Volhard and Fahr state that they form a relatively large proportion of admissions into hospital.

The table shows the relatively great importance of tonsillitis and conditions likely to be associated with persistent streptococcic infection such as the influenza-like diseases, otitis media, and sinus infection in the causation of the end stage of diffuse glomerulonephritis as well as the infrequency with which the end stage occurs in cases due to scarlet fever.

PREDISPOSING CAUSES.—Heredity.—Almost all authors have mentioned instances in which nephritis has occurred in several members of the same family. Thus, Eichhorst mentions a family in which nephritis occurred in the grandmother, mother, two sons, and one daughter. In one family observed by Herrick there was a history of renal trouble in the parents and several uncles and aunts. In Volhard and Fahr's series there was nephritis in the sibs of two families, so that an hereditary tendency to the development of nephritis has come to be a well-recognized fact.

Cold.—This condition formerly occupied much the same position in the etiology of nephritis that it did in the causation of pneumonia. This was based on several apparent facts. Exposure to cold frequently appears in the anamnesis of cases of nephritis. The opinion prevailed that there was some mysterious relation between the kidney and the skin. Siegel claims to have produced nephritis in dogs by exposing the feet to cold water. There are many facts to discount cold as more than a predisposing factor in the production of nephritis. Thus careful analysis of the so-called cold nephritis will show an infection along with the cold. Experimental results of the application of cold to the skin on the kidney show conflicting results. Koleman-Muller found an

increase of diuresis and Worthheimer a distinct decrease of kidney volume and circulation through the kidney.

Trauma.—This occupies much the same position as a cause of nephritis. The wounds form a focus of infection and a portal of entry for the introduction of bacteria or their toxins into the circulation.

Age and Sex.—An analysis of the cases of true nephritis will show that the great majority of cases occur before the fiftieth year of age and they are more frequent in the male than in the female.

DIFFUSE GLOMERULONEPHRITIS

In adopting the subdivision of diffuse glomerulonephritis into three stages, viz., (1) an acute stage, (2) a chronic stage without kidney insufficiency, and (3) an end stage of chronic diffuse nephritis with kidney insufficiency, it is necessary to call attention to some facts which Volhard and Fahr have set forth in connection therewith.

Transitional cases occur which sometimes render a sharp differentiation from the end stages difficult or impossible, while the symptoms of those cases at either end of the series are characteristic enough. Also mixed types of renal disease occur which may obscure the clinical picture.

The outcome of an acute glomerulonephritis which does not heal is a chronic glomerulonephritis. It cannot be stated definitely how frequently this occurs, but depends largely upon the early recognition and proper treatment of the acute stage. It occurs not only in the severe cases, but also in mild cases. Rarely, especially in the severe cases of extracapillary nephritis, is the process so severe as to preclude the possibility of recovery. The glomeruli may be diffusely involved in the inflammatory process and the functional capacity as a whole sufficient as measured by the usual functional tests. So there may be cases of chronic glomerulonephritis which may exist for a long time without impaired functional capacity. There are other cases of chronic glomerulonephritis which by regeneration of the injured part and overwork of the preserved secreting portion may for a long time compensate the destroyed portion. Thus cases may occur, showing for a long time impaired function before passing over into fatal insufficiency.

The separation of the chronic forms is therefore made on a purely functional basis. This does not depend entirely upon the length of time in which the disease has existed. The end stage may arise directly from the acute stage, especially in the severe extracapillary forms of the disease or gradually through the second stage over a long period of time. Nor does the subdivision of these cases depend upon the macroscopical anatomical condition of the kidney, as the function may be preserved in a contracted kidney and markedly impaired in a large kidney. Yet the histological examination offers some grounds for the judgment as to function. This depends largely upon the extent to which the normal architecture of the kidney has been destroyed. The most characteristic features of this are the destruction of large numbers of

glomeruli and tubules with widening of the remaining tubules lined with flat endothelial-like epithelium, which gives rise to the characteristic diuresis of this stage—polyuria with low fixed specific gravity. The kidney is no longer able to concentrate. Volhard and Fahr in adopting the old classification of Frerichs, emphasize the fact that they do not do so on a macroscopic-anatomical basis, but on a functional basis purely. In the second stage the kidney may already be contracted and in the third stage the kidney may be smooth or indeed enlarged; nevertheless, the greater number of cases of the third stage show secondary contracted kidney anatomically.

Acute Diffuse Glomerulonephritis

Symptomatology.—CLINICAL HISTORY.—It is well known that acute nephritis following scarlet fever frequently shows a distinct period of incubation, usually coming on in two or three weeks after the infection. This may also be seen in those cases developing from diphtheria and tonsillitis.

The general symptoms of onset are frequently slight and may be overlooked if edema is not associated with them or misinterpreted unless the urine is examined as a routine. The patient may complain of fatigue, exhaustion, anorexia and increased thirst, or the disease may set in more stormily with chill, fever and vomiting. Eclamptic uremia not infrequently occurs, especially in children, and this occurs independently of the severity of the kidney lesion. Slight degrees of dropsy and markedly increased blood-pressure predispose to convulsions. It is less frequent in those cases accompanied by high grade dropsy, *i.e.*, complicated with nephrosis. True uremia, or that characterized by the symptoms of urinary poisoning, rarely occurs in the acute form, probably due to the fact that the nephritis is usually not so severe as to lead to severe kidney insufficiency.

PHYSICAL FINDINGS.—*Blood-pressure.*—Increased blood-pressure is a characteristic feature of diffuse glomerulonephritis. Its presence in an acute kidney disease establishes the diagnosis of acute diffuse glomerulonephritis unless it be a necrotizing nephrosis associated with anuria. The pressure may be but little above normal or not at all raised in the mildest cases, as also when the nephritis is associated with conditions such as general sepsis and toxic cardiovascular weakness which prevent a general vascular reaction. It may set in rapidly and disappear early, or, as is more frequently the case, rise gradually and recede gradually. While the highest pressures usually correspond to the height of the disease as indicated by the urinary findings, the maximal pressures cannot be said to run parallel to the severity of the disease. In the author's cases the systolic pressures have varied between 130 and 200. Volhard and Fahr saw in 67 cases values from 140 to 160 twenty times, higher values twenty-one times and lower values twenty-six times.

Frederick von Müller expresses the opinion that the same toxic substances that produce uremia may, in lessened concentration, effect the

vasomotor center, thus causing a heightened blood-pressure. Ophüls states that the rise of pressure in the subacute form of glomerulonephritis is possibly due to the irritative effect of the same substance or substances which cause the damage to the endothelium of the blood-vessels, the irritation causing an increased tonus in the arterioles all over the body, which forces up the general blood-pressure. The rise of pressure certainly precedes any noticeable general anatomic changes in the small arteries, and may persist for long periods without being followed by any such change. Whether or not the irritation is to be followed by anatomic changes appears to be purely accidental.

Hewlett states that the hypertension of acute nephritis is probably not due to anatomical changes in the heart or blood-vessels. The rise in pressure may be quite rapid and has been observed within forty-eight hours after the onset of an acute nephritis. This, together with the subsidence of the high blood-pressure as the disease improves, indicates that the elevated pressure is due to changes in function rather than in structure. Although direct evidence is lacking, it seems probable that the acute hypertension in such cases is due to a general constriction of the systemic arterioles. Whether this constriction is caused by nervous reflexes from the diseased kidneys, or whether, as seems more probable, it is due to toxic substances, is not known.

It is generally conceded that glomerulonephritis in contradistinction to tubular nephritis is associated with hypertension, and Volhard and Fahr hold that those nephropathies associated with diffuse glomerular changes are associated with increased blood-pressure. As will be seen from the microscopical findings in the kidney of acute diffuse glomerulonephritis, the glomerular capillaries as well as the *vasæ afferentiæ* are more or less empty of blood, especially during the height of the disease. Volhard assumed that this was due to an angiospastic ischemia. Recently Walter Hülse from Volhard's clinic has brought evidence which strongly supports this theory and demonstrated the fact that the capillaries of the glomeruli as well as the arterioles of the kidney show an increased tonus in acute nephritis. In two cases of clinically acute diffuse glomerulonephritis which came to autopsy, the kidneys were slightly smaller, the capsules stripped easily, the outer surfaces were smooth and small hemorrhagic points were visible. On section, the cortices were swollen, of a clear brownish color, and well differentiated from the medulla. They presented a parboiled appearance; the markings were obscured. Microscopically, the glomeruli were rich in nuclei, containing on an average of from 50 to 70 leukocytes. The endothelial nuclei were large, swollen, and increased in number. The glomerular capillaries were widened and filled with loose granular masses in which a rare blood-cell was enclosed; here and there was a glomerulus whose capillaries were completely filled with red blood-cells and here the capillaries themselves were almost completely hyalinized.

In the other loops there was only occasional hyalinization. The *vasæ afferentiæ* did not contain any blood, were partially widened and contained coagulated plasma. The intertubular capillaries were almost

wholly empty of blood. The small veins were distended with red blood-cells. It was supposed that if this closure of the vessels were due to increased functional tonus during life, at death this would disappear and it would be possible to inject them under a pressure which did not exceed the blood-pressure during life. Hülse was successful in this in both cases, whereas in a case of diffuse glomerulonephritis with subacute course, marked endarteritis, a blood-pressure of 210 mm. Hg., and which ended from kidney insufficiency, the vessels could not be injected, showing that the closure was of an organic nature. Hülse concluded that the cause of the ischemia in the first stages of acute diffuse glomerulonephritis is not organic, but due to functional spasm which involves the capillaries of the glomeruli as well as the arterioles of the kidney.

Whether the anatomical changes which occur in the vessels and glomeruli in the further course of diffuse glomerulonephritis are to be regarded as the result of this increased tonus must be determined by further examinations. It may be assumed that the arterioles in other parts of the body are similarly affected. The actual cause of the constriction remains undemonstrated.

The Heart.—The findings with respect to the heart vary greatly. In cases with high blood-pressure and slight edema, the apex beat may be displaced downward and outward, the area of cardiac dullness increased, the second aortic sound accentuated, and a presystolic gallop rhythm and a systolic murmur at the apex may be present. Indeed, in rare cases, marked dyspnea and edema of the lungs, the result of cardiac dilation, may dominate the clinical picture. As a rule, however, no signs of cardiac hypertrophy or dilatation can be made out. This is especially likely to be true in the cases combined with nephrosis. It is now generally agreed that the cardiac hypertrophy is the result of the increased work, produced by the increased peripheral resistance. It is said that if an increased arterial pressure lasts for more than four weeks, an hypertrophy of the heart develops.

Edema.—Edema has long been considered a cardinal symptom of acute nephritis. It will be seen from the foregoing, that it is to be regarded as a manifestation of nephrosis rather than nephritis. Many cases of acute nephritis run their course, end in recovery or death in the acute stage or pass over into the chronic stage and finally result in death from kidney insufficiency without showing any edema. Volhard and Fahr have shown by comparing the clinical with the anatomical findings that there is a distinct relationship between the dropsy and the hyalin granular and fatty degeneration of the epithelium of the proximal convoluted tubules, and hold that when dropsy, to any considerable extent, occurs in acute diffuse glomerulonephritis, marked evidence of degenerative changes in the tubular epithelium is present. They designate these as the "mixed type," nephritis plus nephrosis. They state further that about one-half of the cases will show this mixed type. Slightly more than 50 per cent. of the author's cases have shown clinically the combination of nephritis and nephrosis. Slight puffiness

of the eyelids or moderate degree of generalized edema not infrequently occurs.

The Eye-grounds.—Changes in the eye-grounds are not nearly so frequent in acute as in chronic nephritis. A true papillitis may be present, and the true albuminuric retinitis is not infrequently found in the cases associated with pregnancy and excessive blood-pressure, as well as hemorrhages into the retina.

LABORATORY FINDINGS.—*Blood.*—Although the patients usually present a pallor of the skin, the blood examinations do not regularly show an anemia. An hydremia is not infrequently present and those cases accompanied by severe dropsy show the clinical and physical changes in the blood-serum described in nephrosis.

Urine.—The color of the urine varies greatly according to the presence of blood. The latter is usually present, especially in the beginning of the process and gives to the urine a smoky appearance. It may also be present in the decline of the process, which indicates an opening up of the blood passages—the glomerular loops—which as a result of the inflammation had become bloodless. Sometimes the blood is recognizable only on microscopical examination. In the absence of blood, the urine is usually paler than normal. The reaction is almost always acid. The quantity is usually greatly diminished. An oliguria of a few hundred cubic centimeters in twenty-four hours may be present and in the severe cases anuria may occur. The specific gravity is usually below normal—the lower it is with oliguria the more severe is the injury to the kidney. Albumin is generally present and varies greatly in quantity. It is of course abundant in the presence of macroscopical blood, and also tends to increase as the nephrotic element enters more prominently into the case. It also increases with the occurrence of eclamptic uremia. In the absence of blood, the purer the glomerulonephritis process the less the quantity of albumin. In some very severe cases albumin may be present only in a trace or, indeed, absent. The sediment will show on microscopic examination red blood-cells, casts of various kinds, and frequently bacteria. In the cases complicated with nephrosis fatty epithelium and double refracting substance may be found. Not infrequently the patient complains of pain and tenderness on voiding. Nycturia may also be present, due possibly to the nocturnal elimination of edema.

SPECIAL EXAMINATION.—*Functional Tests.*—The functional capacity of the kidney in acute diffuse glomerulonephritis varies greatly according to the severity and character of the lesion. The ability to excrete water is often not at all impaired and indeed may be excessive with disappearing edema. On the other hand, the excretion may be prolonged or markedly diminished. The same obtains with reference to the ability to excrete salt. The ability to concentrate may be good or impaired. The urea or non-protein nitrogen in the blood is often within normal limits. Slight excesses are, however, not infrequent, and indeed high values may be found. The same variations may be found with respect to the excretion of phenolsulphonephthalein.

Complications and Sequelæ.—Secondary infections do not play such a prominent rôle in pure acute glomerulonephritis as in nephrosis, but erysipelas, pneumonia, pleurisy and meningitis may occur as complications. The outcome of those cases not ending in recovery is chronic glomerulonephritis. With respect to the association with other diseases and the types of the disease it is only necessary to repeat what has been said with reference to the association with nephrosis and the description of the clinical history.

Treatment.—**PROPHYLAXIS.**—All of those conditions which may give rise to acute diffuse glomerulonephritis should receive careful consideration and appropriate treatment. While every focal infection does not produce an acute nephritis even where they are found definitely to exist, they should, if possible, be removed. In the discussion of the etiology of nephritis we have seen the important part which infections about the pharyngeal ring play in the production of nephritis. Possibly many tonsils as well as teeth are unnecessarily sacrificed, but all cases of acute nephritis should be referred to those competent to investigate and treat tonsils, sinuses and teeth. The Lyon-Meltzer method of investigation of the gall-bladder has shown it to be a point of focal infection and it should receive appropriate treatment, as other foci of infection in the gastro-intestinal and genito-urinary tracts. The kidneys should be safeguarded in all cases of scarlet fever. Frequently a **milk diet** and a **saline purge** will, in these cases, prevent the development of a nephritis. These cases should receive especial care during convalescence. The possibility of the development of nephritis in other infections, such as infected wounds, acute rheumatic fever, respiratory infections, malaria, as well as in pregnancy, should be kept in mind and proper care and treatment of these patients carried out.

The lesson taught by the convalescent camps of men discharged from duty during the World War should be utilized by the civil practitioner. When it is shown that in young men of strong constitutions it requires for complete recovery from scarlet fever 77 days, from tonsillitis and sinusitis 34 days, from diphtheria 57 days, from pneumonia 58 days, and from acute tonsillitis 36 days, it will be realized how remiss we have been in relinquishing care of these patients too early.

The indications for the treatment of acute diffuse nephritis are: (1) The removal of the cause when possible, (2) the protection of the kidneys, (3) treatment of complications, and (4) supervision of convalescence.

The cause of acute diffuse nephritis is frequently ascertainable and often capable of being removed. The removal of focal infections, the treatment of diphtheria and malaria, and after careful consideration the termination of pregnancy, etc., are in many of these cases the primary indications.

The protection of the kidneys includes a consideration of rest, environment, diet, and the regulation of fluid and salt intake, and the stimulation of other organs capable of relieving the work of the kidneys.

Rest is the first essential in the treatment of acute nephritis. As soon as the condition is discovered, the patient should be placed at **absolute rest in bed**. There should be plenty of fresh air in the room, but protection from chilling and draughts is necessary. Protected by such clothing as will promote the action of the skin, a part of each day with the patient in the **open air** is desirable. It is often difficult to decide as to how long the bed rest should be continued. Here the best criteria are possibly the condition of the urine as to blood and that of the kidney as to function. Von Noorden has long advised that the presence of blood in the urine was an indication to keep the patient in bed. As a general rule this advice should be adhered to, but we sometimes meet with cases in which hematuria persists and in which the renal function is good. The general condition of such patients, as a result of prolonged rest in bed, may seem to come to a standstill or show distinct evidences of growing worse. In such cases short intervals out of bed each day, with careful watch as to the hematuria and renal function, will result in general improvement. Again other cases are met with in which the blood disappears from the urine, but the kidney function continues impaired. In such cases, rest in bed should be continued unless the general condition seems to be made worse by confinement to bed, when the patient may be allowed to be up a part of each day, exercising the same caution as described above with reference to persistent hematuria. The average case will require a period of from two to six weeks in bed. The return to normal activity should be gradual and controlled by the examination of the urine and the determination of the kidney function.

Von Noorden has pointed out that protective therapy in general is intended in the first place to save the diseased organ all superfluous work, and in the second place to eliminate all those irritants from the diet that might stimulate it to increased effort; but it must always be remembered that protective therapy directed toward sparing one organ should never go so far as to indirectly damage some other organ or the organism as a whole. Hence, while the kidney should be protected by a **low protein diet**, this should contain sufficient caloric value and balance to maintain the nutrition of the patient.

Where the onset is with severe nausea and vomiting, all food by mouth should be withheld and one pint of a 20 per cent. **glucose solution** administered by the drip method **by rectum** every eight hours. Water is necessary in this condition to prevent injurious dehydration of the body. In those cases associated with marked kidney insufficiency the protein should be eliminated from the diet entirely for a short time. The protein-free diet advised by Chase serves very well here. "The juice of one-third lemon, one teaspoonful of cane sugar, six tablespoonfuls of milk sugar, and one glass of water mixed well, may be taken four times a day." This should not be continued more than three or four days consecutively, for after this time on this diet, the patient will begin to draw on his own body proteins. In the average case, the articles of food suggested by Von Noorden may be used. These are milk, rice,

groats, maizina or other cereals (made into soup, porridge or pudding with a part of the milk and cream, and with butter and sugar), bread, and fruit juices, particularly sterilized grape juices. The following menu given by Von Noorden may serve as an example from which similar diets may be constructed by any one by reference to any of the numerous food lists with their nutrition value:

Milk (skimmed)	1500 c.c.
Cream	375 c.c.
Rice	50 grams.
Zwieback	50 grams.
Butter	50 grams.
Sugar	20 grams.

This menu contains 2,900 calories. This diet should, however, not be continued for too long a period—possibly not longer than a week or two. With the improvement of the patient the protein content of the diet may be increased, but possibly to not more than 70 grams, in the form of meats, milk, eggs and vegetable proteins for the average man, until all evidence of nephritis has subsided. In the construction of this diet, at this time, due consideration should also be given to its content in carbohydrates, mineral ash and the necessary food substances of unknown chemical nature, the fat soluble A and the water soluble B. All of these substances may be supplied in meat, eggs, the seeds, tubers and green leaves of plants, dairy products and water. Especially during convalescence the difficulty will arise in giving the patient such directions as he is able or willing to carry out to fulfill these requirements. The patient will rarely take the trouble to weigh out the articles of food furnished him. Dr. O'Hare has rendered a great service in the construction of a diet sheet which the patient can use at home and obtain the required constituents of a balanced diet, with great variety and by the use of home measures. The diet sheet is this:

O'HARE'S DIET SHEET

Any combination of the foods designated below may be selected.

Foods not listed below must not be taken.

In Groups I and II there is restriction in total amount.

The foods in these groups must be served in full or half portions.

A full portion in Group I counts one. (One is equivalent to approximately 4 grams of prôtéin.)

A full portion in Group II counts two.

In Group III the quantity of each is not restricted, although you are urged to use discretion.

Your total score for the day should be ____.

Your total amount of fluid should be ____ pints.

Do not add salt or spices to the food after it has been cooked.

GROUP I

(Each full portion counts 1)

<i>Breads</i>	<i>Full portion</i>	<i>Vegetables</i>	<i>Full portion</i>
Bread (white)	1 average slice	Baked beans	1 tablespoonful
Bread (graham)	1 average slice	Lima beans	1½ tablespoonfuls
Uneda biscuit	5 crackers	Potato, creamed	1 tablespoonful
Shredded wheat	1 biscuit	Potato, mashed	1½ tablespoonfuls
		Potato, boiled	1½ tablespoonfuls
<i>Cereals</i>		Green peas	2 tablespoonfuls
Oatmeal	2 tablespoonfuls	Canned corn	2½ tablespoonfuls
Boiled rice	3 tablespoonfuls	Onion, boiled	3 tablespoonfuls
Cornmeal mush	4 tablespoonfuls	Macaroni	4½ tablespoonfuls
Cream of wheat	6 tablespoonfuls	Squash, boiled	5 tablespoonfuls
Farina	6 tablespoonfuls		

GROUP II

(Each full portion counts 2)

<i>Dairy Products</i>	<i>Full Portion</i>	<i>Meats</i>	<i>Full Portion</i>
Milk	1 glass	Chicken, roast	3" x 3" x 1½"
Egg	1 egg	Lamb chop, broiled	¾ chop
Eggs, scrambled	1½ tablespoonfuls	Lamb, roast	3" x 2½" x 1¼"
Custard	3 tablespoonfuls	Beefsteak, broiled	2" x 1" x 1"
<i>Fish</i>			
Cod, boiled	1" x 1" x 1½"		
Haddock, boiled	1½" x 1" x 1"		
Oysters	7 oysters		

GROUP III

(No restrictions)

<i>Vegetables</i>	<i>Fruits</i>	<i>Miscellaneous</i>
Turnips	Watermelon	Sugar
Carrots	Plums	Syrup
Cabbage	Pears	Candy
String beans	Peaches	Honey
Cucumbers	Strawberries	Maple sugar
Cauliflower	Grapes	Butter
Celery	Apple sauce	Cornstarch
Tomatoes (fresh)	Grapefruit	Arrowroot
Tomatoes (cooked)	Raspberries	Tapioca
Lettuce	Blueberries	Post Toasties
Asparagus	Muskmelon	Maple syrup
	Apples	Olive oil
	Pineapple	
	Prunes	
	Oranges	

The patient should keep a record of his daily menu and submit it to his physician from time to time in order that the latter may determine whether or not he is getting the required number of calories to maintain his nutrition.

When acute diffuse glomerulonephritis is associated with nephrosis or in the absence of the latter the kidney is impermeable to water, the fluid intake should be markedly restricted. On the other hand, when the kidneys respond with diuresis to the fluid intake, as they will not infrequently do, there is no indication for the restriction of water. Such an amount of water as will fix the total intake at 1500 to 2500 c.c. may be allowed.

The conditions are very similar in respect to the allowance of **sodium chlorid**. Where marked edema is present the case should be managed just as one of nephrosis (*vid.*). However, in some cases in which edema is not present, the kidneys will not excrete salt well; in such cases, the salt should be restricted. In any case it is well to insist that the patient does not add extra salt after the food is cooked.

DIURETICS.—Speaking of diuretics in acute nephritis, Von Noorden many years ago said, “I regard such prescribing as radically wrong. These stimulants are, so to speak, whip-lashings. It would be the greatest paradox to economize the work of the kidneys to the utmost possible extent in one direction, and in the other to excite them to increased activity by means of the strongest stimulants we possess.” More recently Christian and his co-workers have brought experimental as well as clinical proof of the ineffectiveness and possibly the harmfulness of diuretic drugs in acute nephritis as well as in all other uncomplicated forms of nephritis.

In the absence of complications, diaphoretic measures and drugs are not called for; neither are drastic cathartics. Only mild laxatives to secure the necessary daily bowel movements are indicated. For this latter purpose **cascara**, **phenolphthalein**, **petrolatum** or mild salines like **sodium phosphate** are sufficient.

TREATMENT OF COMPLICATIONS.—The management of edema, uremia and myocardial insufficiency is that described in the chapter on nephrosis, uremia, and circulatory nephropathies (*a.v.*).

SUPPRESSION OF URINE.—This disquieting complication may accompany marked edema in cases associated with nephrosis, set in with uremia in severe cases, or it may exist for some time with few or no toxic symptoms. Its occurrence under the first two conditions has been discussed. What to do in the last case is often a difficult matter to decide. Many, following the lead of Martin H. Fischer, have claimed successful results from the administration of **Fischer's solution** intravenously with or without previous bleeding. While the author has seen good results from this procedure in necrotizing nephrosis, as in suppression of urine in bichlorid of mercury poisoning, it has always been without results in the few cases of acute diffuse glomerulonephritis in which he has tried it. His own experience has rather been in accord with that of Christian, and he believes that his advice, as that of Von Noorden, is the better; *viz.*, to **restrict the diet** to the milk-sugar mixture, the **fluids** to not more than 800 or 1000 c.c. in the twenty-four hours, to **apply heat** to the **lumbar region** and if toxic symptoms begin to appear, to use **diaphoretic measures**, **cathartics** freely and, according to the condition present, **phlebotomy**.

CONVALESCENCE.—The diet may now be increased in order to build up the general condition of the patient. The protein content of this, however, should not exceed 100 grams per day for the average man. In anemic cases the administration of iron in the form of **Bland's pills** or **liquor ferri et ammoniac acetatis** will be of advantage. The permeability of the kidney for water should be tested at intervals and when

it is good, the advice of Von Noorden to administer large quantities of fluid is of value. If convalescence does not progress satisfactorily, a **sojourn** at the Gulf Coast, the table lands of Arizona and New Mexico or the foot-hills of Southern California may be of benefit.

Prognosis.—The prognosis of acute diffuse glomerulonephritis is immediately good as to life. Most of the patients completely recover. Death may rarely occur from insufficiency of the kidney as a result of the severity of the injury to the kidneys. Associated conditions as the causative sepsis or myocardial insufficiency may result fatally. Complications or secondary infection such as erysipelas, pneumonia, pleurisy, and meningitis may render the prognosis grave.

As to whether the acute will pass over into chronic diffuse glomerulonephritis will depend mainly upon three factors; *viz.*, the extent of injury sustained by the kidney, the time of recognition, and the treatments.

Pathology.—The macroscopical appearance of the kidneys varies greatly. This is due largely to variability of the serous infiltration, the quantity of blood in Bowman's capsules, the tubules and capillaries and the amount of fatty degeneration present. The weight of the kidney varies from normal to 190 grams. The consistency depends largely upon the amount of serous infiltration present. On incising the capsule the substance may well out. The capsule strips easily, the surface of the kidney is smooth and small pin-point or pin-head sized hemorrhages are almost always to be observed.

In cases where the capillaries are markedly filled with blood and there is much extravasation of the blood into Bowman's capsule and the tubules, the color is brown. With empty capillaries the color tends more to grayish brown and the gray tone may be increased by the pressure of fatty degeneration in the epithelium of the tubules. On cut surface the conditions as to color are much the same as that of the outer surfaces. The cortex and medulla are sharply differentiated from each other, the pyramids being quite dark. The cortical markings are often recognizable but may be obscured. The cortex appears as if cooked. With proper light the glomeruli may be seen as small pale translucent points projecting above the cut surface.

The microscopical appearance is more constant and typical. The criteria are lengthening and widening of the capillary loops of the glomerulus, anemia of the loops and particularly the increase of cells of polynuclear and endothelial types inside the loops.

The glomerular epithelium may show swelling, desquamation and proliferation. According to Löhlein the loops of the glomerulus are usually empty of blood and Fahr confirms this in the fully developed stage, but holds that in the fresh stages the loops may be filled with blood. There may be a disproportion between the amount of blood in Bowman's capsule and the uriniferous tubules.

The contents of the capsular space varies. In some areas there may be desquamated epithelium or red and white blood-cells, or both, while in other areas there is only coagulated albumin. Occasionally

fibrin is also seen. In many areas adhesions between the two layers of the capsule may exist.

The tubular epithelium varies as to whether the glomerulonephritis is associated with nephrosis, with which there is diffuse and widespread granular and fatty degeneration involving chiefly the epithelium of the proximal convoluted tubules. Without nephrosis the appearance of the tubular epithelium varies according to the stage and degree of the nephritis. Those proximal convoluted tubules in connection with the more severely affected glomeruli may show fatty and granular degeneration. Pure hyalin casts are rare in Henle's loops and the collecting tubules, while conglomerate masses consisting of coagulated albumin, red and white blood-cells in the form of casts are quite numerous.

The interstitial tissue of the kidney shows very slight round cell infiltration in fresh cases, while in more advanced cases it may be quite marked.

ILLUSTRATIVE CASE No. I.—Dr. C. F., white, male, age 40, physician. Seen at his home in Mississippi, January 15, 1921.

Chief Complaint.—Fever, general rachialgia, nausea, vomiting, duration three days.

Family History.—Negative.

Past History.—Has had no previous illness except an attack of cystitis of short duration about fifteen years ago.

Present Illness.—Three days ago he had a rigor which was accompanied and followed by fever; some difficulty in voiding urine, general rachialgia, nausea and vomiting.

Physical Examination.—The patient is well nourished. Height about 5 feet, 10 inches; weight 190 lbs. Temperature 101.4° F. (38.55° C.). Pulse 96 per minute, full and regular. Blood-pressure 160–90. Head, neck and lungs show no abnormalities. Heart, point of maximal impulse in the fifth intercostal space 8 cm. (3.14 ins.) from the midsternal line. No enlargement of the supracardiac area of dullness. The aortic second is possibly a little accentuated. There are no murmurs present. The *abdomen* is without abnormal findings. There is no tenderness in either costovertebral angle. The examination of the nervous system is negative.

Urine.—Single specimen, though it is stated that the twenty-four hour quantity is scant. Dark, amber; specific gravity 1025; albumin, a trace; sugar, negative; microscopical, hyalin, granular and composite casts; a few leukocytes; rather numerous red blood-cells; bacteria, cocci and motile bacilli.

Blood.—Polymorphonuclears 88 per cent.; small lymphocytes 5 per cent.; large mononuclears 7 per cent. Blood urea 48.5 mg. per 100 c.c. Under rest in bed, low protein diet and laxatives, he rapidly improved. On January 24, 1921, blood-pressure 140–80; urine, no albumin,

a rare cast, no pus or red blood-cells; blood urea 31.5 mg. per 100 c.c. Under two months' rest from practice, a diet not exceeding 80 grams of protein per day and a trip to Cuba, he felt perfectly well and fit. Urine negative, blood-pressure 138-70. About the first of June, after getting wet in a rain, he had an attack, somewhat similar though not so severe, as the one in January. On July 21, he was in the author's office when he felt quite well, though the blood-pressure was 155-80; the single specimen of urine voided, was clear, yellow, acid, specific gravity 1024; albumin and sugar, absent; a few hyalin and granular casts, a few leukocytes and epithelial cells, no red blood-cells. Phenolsulphonethalein output in two hours and ten minutes, 80 per cent. Blood urea 24 mg. per 100 c.c.

Diagnosis.—Recurring acute diffuse glomerulonephritis.

ILLUSTRATIVE CASE No. II.—B. W., negro, male, age 35, laborer.

Anamnesis.—Family history, negative. Past history, negative except there was a sore on the penis last year, which was not followed by secondary manifestations of lues. About July 1, 1917, he complained of pain in the third finger of the right hand. The pain, which was dull and throbbing in character, grew progressively worse. At the end of the week his doctor made an incision in the finger on the palmar surface. No pus was obtained. The condition of the finger grew rapidly worse. Patient says that the bone rotted and became unjointed. About this time the entire hand and arm became swollen and he had high fever. About three weeks after the first incision was made the finger was amputated. After this there was gradual improvement. Two or three weeks later patient stated that he began to have shortness of breath, that his feet, legs and abdomen began to swell. This had progressively increased and on this account he was admitted to the Memphis General Hospital, September 12, 1917.

Status Præsens.—Well-developed. There is marked general edema, including external genitalia. The third finger on the right hand is absent, amputated at the metacarpophalangeal joint. Healing perfect, though the hand is swollen and stiff.

Heart.—The apex was not located. The area of cardiac dulness extends 10 cm. (4 ins.) to the left of the midsternal line. There is a soft systolic murmur at the apex, not transmitted. The pulmonic second sound is slightly accentuated.

Lungs.—Negative, except for the presence of fluid in both pleural cavities, more in the right than in the left.

Abdomen.—Ascites. Neither liver nor spleen palpable.

Temperature.—97.8° F. (36.55° C.). Pulse 64. Respiration 24.

Urine.—September 13, 1917, pale; specific gravity, 1010; albumin, heavy; casts; pus cells. September 25, 1917, pale; specific gravity, 1010; albumin, heavy; hyalin and granular casts; no pus cells. October 17, 1917, dark straw-color; specific gravity, 1014; alkaline; albumin, heavy;

no casts. October 18, 1917, dark straw-color; specific gravity, 1014; alkaline; albumin, heavy; no cast. November 11, 1917, pale; specific gravity, 1010; alkaline; albumin, heavy; no casts.

Blood.—October 10, 1917, leukocytes, 7400 per cm.; November 12, 1917, erythrocytes, 4,200,000; leukocytes, 6400; polymorphonuclears, 63 per cent.; small lymphocytes, 34 per cent.; large mononuclears, 3 per cent. Wassermann, negative.

Blood-pressure.—September 21, 1917, systolic, 190; October 8, 1917, systolic, 172, diastolic, 118; October 16, 1917, systolic, 170, diastolic, 115; November 5, 1917, systolic, 145, diastolic, 90.

Functional Tests.—Mosenthal kidney-test diet, November 8, 1917, with disappearing edema.

URINE EXAMINATION

Time of Day	Quantity	Specific Gravity	NaCl		Nitrogen	
			Per Cent.	Grams	Per Cent.	Grams
8-10 A. M.	280 c.c.	1010				
10 A. M.-12 M.	225 c.c.	1009				
12 M.-2 P. M.	215 c.c.	1011				
2-4 P. M.	325 c.c.	1010				
4-6 P. M.	200 c.c.	1008				
Total day	1495 c.c.		.76	11.362	.9	13.45
Total night	1244 c.c.	1008	.8	9.952	.85	10.57
Total 24 hours	2739 c.c.			21.314		24.02
Intake H ₂ O	1760 c.c.			8.5		13.4
Difference	979 c.c.			12.79		10.62

Weight	Period	Blood	Urine				Ambard's Co-efficient
			Period	24 hrs.	Urea Grams	24 Hours Per Cent.	
65.1	4-6 P. M.	48 mg. per 100 c.c. urea	200 c.c.	2400 c.c.	33.6	14	.09

Phenolsulphonaphthalein (intravenously) 50 per cent. in two hours. CO₂ tension alveolar air 30 (Marriott). R. ph. 8.2 (Marriott).

Diagnosis.—Acute diffuse glomerulonephritis plus nephrosis.

ILLUSTRATIVE CASE No. III.—W. F., male, negro, age 23, laborer. Admitted to Memphis General Hospital March 3, 1921; discharged improved April 4, 1921.

Chief Complaint.—Shortness of breath, pain in the abdomen, swelling of abdomen. Duration of symptoms, two weeks.

Family History.—Father was alive and well at 75 years of age; mother, 45, alive and well. Seven sibs, five alive and well, two died in infancy.

Past History.—Used tobacco moderately and whiskey occasionally. Also coffee moderately. Had Tripper two years previous; rheumatism (!) two years ago; several attacks of sore throat and sore mouth; ma-

laria, one year ago; dislocation of wrist, five years ago; burn above the left elbow one and one-half months ago, infected.

Present Illness.—Three days before the onset of symptoms, he noticed that his urine was high colored (red), and that he voided from 3 to 4 times during the day and from 8 to 10 times during the night. Onset with chill while eating his lunch. The chill lasted several hours and he felt chilly for two days. The chill was followed by fever and profuse sweating, but he had no nausea or vomiting. He was unable to work. The day following the chill he took calomel and oil with good results. On that day he went to work at 1 P. M. During the afternoon he became wet, went to bed, but felt well. That night and for several nights following, he had night sweats which lasted from 12 P. M. to 5 A. M. On the next day he had headache, but felt fairly well and arose from bed. On the fifth day, he noticed some swelling of the feet and ankles. Two days later, he noticed that his eyes were puffed in the morning and later the whole face. His legs and feet swollen, but the swelling subsided some at night. Then abdomen began to swell. His bowels moved every morning. His appetite was good. His nights were restless. At the time of his admission his urine was clear. Frequency, day from 3 to 4 times, night 2 times. There is no burning or straining on voiding. Two weeks after onset of anasarca he began to have shortness of breath and cough. Dyspnea and cough became so severe that he had to sit up to breathe. Two days before admission he began to bring up frothy sputum streaked with blood. Since onset he has also had some dizziness; pain in his right knee and ankles. Lately he has had fever and no night sweats in over a week.

Physical Examination.—The patient is a well-developed and well-nourished negro man apparently 25 years of age. His color is black, frame large and expression good. He is resting comfortably in bed. He coughs occasionally and brings up blood-streaked sputum. There is edema of face, head and lower extremities. There is a fine scaling of the skin which is hot, dry and of fairly good texture. *Eyes:* Muscles are good, scleræ of a slightly yellow tinge, the pupils were equal and reacted to light and distance. *Nose:* Flat, a typical pug-nose. Nasal cavities are negative. *Mouth:* Lips were fissured; a pigmented rim around the edge of the gums; the teeth were fair; the tongue was clear, no tremor; the throat was negative. *Neck:* No visible superficial veins, no masses felt, contour normal, no tracheal tug. *Chest:* Expansion on both sides equal. *Lungs:* Excursion good; inspection negative, fremitus normal, no change in the percussion note anteriorly, slightly impaired on the left posteriorly in the region of the angle of the scapula where it approached dullness. Wheezing respiration, râles generalized, but especially numerous in the left infraclavicular region; moist râles over both bases; breath sounds audible over chest, with bronchovesicular breathing at the angle of the scapula with increased voice sounds. *Heart:* Apex not visible; point of maximal impulse in the fifth interspace in the midclavicular line; apex beat of good force but fast, no thrills, cardiac dullness not enlarged, sounds clear, not accentuated, no murmurs. *Abdo-*

men: Contour normal, distended, round, uniformly tympanitic, no masses, kidneys, liver nor spleen palpable. **Extremities:** Edema of feet, ankles, legs, knees and hands. Scar with healed area and two small unhealed areas about left elbow due to a burn; the tissues around the elbow were indurated; there was limited motion of the elbow due to pain in healing areas; traumatic deformity of the left wrist, fingers were short and stubby and showed evidence of hard work.

Nervous System.—Negative. **Genito-urinary:** Prepuce was redundant, inguinal glands were enlarged.

Course.—From April 5, 1921, bronchopneumonia, fever, quick pulse, gallop rhythm, great dyspnea, frothy, blood-streaked sputum, patchy areas of consolidation; March 29, complete paralysis of extensors of hand and fingers, wrist drop, due to paralysis of right musculospiral nerve. The edema about disappeared and he was discharged to the outpatient department much improved on April 4, 1921.

URINE ANALYSIS

Date	March 4	March 7	March 10	March 11	March 18
Transparency	Turbid	Turbid	Turbid	Turbid	Turbid
Color	Light amber	Light amber	Light amber	Light amber	Light amber
Reaction			Alkaline	Alkaline	Alkaline
Specific Gravity...	1017	1025	1022	1025	1014
Albumin	+++	++++	++	+	+
Sugar	Negative	Negative	Negative	Negative	Negative
Casts	Fine and granular	Many	Many	Many	Many
Leukocytes and pus	++	++++	+	Negative	Negative
Red Blood-cells...	Negative	+++	Negative	Negative	Negative
Quantity				Night 360 c.c.	Day 390 c.c.

BLOOD ANALYSIS

Date	March 4	March 7	March 16	April 1
Red Cells	3,776,000			3,184,000
Leukocytes	7,700	17,500	18,000	5,000
Polymorphonuclears ..	70 per cent.	79 per cent.	90 per cent.	51.5 per cent.
Small Lymphocytes ..	24 per cent.	17 per cent.	8 per cent.	47 per cent.
Large Mononuclears..	6 per cent.	4 per cent.	2 per cent.	5 per cent.
Eosinophils				1 per cent.
Wassermann			++	

FUNCTIONAL TESTS

Date	March 8	March 24	April 5
Phthalein ...	20 per cent. in 1 hour (Intravenously)		
Blood Urea ..	75 mg. per 100 c.c.	38.7 mg. per 100 c.c.	33.3 mg. per 100 c.c.
Creatinin ...	4.15 mg. per 100 c.c.	2.75 mg. per 100 c.c.	2.14 mg. per 100 c.c.

BLOOD-PRESSURE

Date	Systolic	Diastolic
March 4.....	145	115
March 5.....	130	115
March 7.....	146	118
March 8.....	118	88
March 10.....	140	100
March 12.....	145	110
March 16.....	114	108
March 20.....	140	100
March 23.....	140	100
March 24.....	140	90
March 31.....	140	108
April 4.....	122	78

Diagnosis.—Acute diffuse glomerulonephritis, nephrosis, broncho-pneumonia, and paralysis of right musculospiral nerve.

ILLUSTRATIVE CASE NO. IV.—T. J., male, negro, 44 years of age, laborer. Admitted to Memphis General Hospital, November 14, 1919. Died November 30, 1919.

Chief Complaint.—Swelling of feet, legs and abdomen, and shortness of breath on exercise.

Family History.—Negative.

Past History.—Pneumonia at 18; malaria several times in early adolescence, none recently; sore on penis ten years ago; gonorrhea, seven years previous.

Present Illness.—The present trouble began about the middle of September with pain in the left side about the lower border of the ribs. There was also anorexia, general weakness, cough and fever, though he continued his work. This condition lasted about two weeks. The side is still painful to pressure and the pain intensified by forced breathing.

Two weeks ago, his feet and legs began to swell. The swelling gradually ascended and soon the abdomen became distended. He was also troubled with shortness of breath which he says is especially marked when he ascends stairs. He has never had an attack similar to the present. There had been no nausea, no pain in the abdomen and no visual disturbance. He had had some tinnitus; at night has cough and fever. No dysuria; nocturia, from 2 to 4 times for the last two weeks.

Physical Examination.—A negro, male, of large stature. He was well developed and well nourished. He lay on the left side, since lying on the right side caused pain in the chest. *Head:* Pupils equal, regular and reacted to light; mucous membranes presented a bluish discoloration; the tongue was heavily coated and indented on the edges; cerebral

nerves without abnormal findings. *Neck*: The veins are distended and pulsate, especially marked on the right side. *Heart*: Apex beat not seen nor felt. The right border of cardiac dulness was seven and one-half inches to the right of the midsternal line. The left border can not be determined because of the fluid in the left pleural cavity. Heart sounds not heard in the normal area of the apex, but over the ensiform cartilage and to the right of same. They are fairly distinct and there is a slight systolic murmur with point of maximum intensity one-half inch to the right of the ensiform; the sounds at the base are normal. *Lungs*: The respiratory rate is increased and the excursion markedly diminished on the left side; tactile fremitus was absent over the entire left lung; over the same area the percussion note is flat; Traube's semilunar space is obliterated; the breath sounds over the left were distant, but bronchovesicular; there was bronchophony and whispering pectoriloquy in the left inter- and infra-scapular spaces; there were a few diffuse crackling râles throughout the left lung: the right lung was normal except for exaggerated vesicular breathing. *Abdomen*: Showed the presence of considerable free fluid, flatness in the flanks and above the pubes, tympany on top, and a fluid wave; no pain on pressure, viscera could not be palpated. *Extremities*: Scars on right leg, tibial surface, and on back of left arm; the legs and feet are swollen and pitted on pressure. *Lymph-nodes*: There was a generalized adenopathy. *Reflexes*: Were present in the arm; abdominal absent; knee jerks and Achilles present; no Babinski. *X-ray* examinations of the chest showed area of increased density involving the entire left lung crowding upon the right lung, which was also hazy. The blood-pressure was 115-80. Temperature was slightly above normal; pulse 96; respiration 30. Specific gravity of urine 1020, acid, albumin; red blood-cells.

Course.—During the stay in the hospital there was slight fever with periods of apyrexia. November 21 the abdomen was tapped; 660 c.c. of a slightly cloudy fluid with a specific gravity of 1010 was obtained. The non-protein nitrogen of same was 193 mg. per 100 c.c. On November 28, 1080 c.c. of bloody fluid was aspirated from the left chest. For several days before death, there was marked asthenia, somnolence, twitching of the muscles, hiccup and urinous odor of the breath. He had a left otitis media. The patient died November 30, 1919.

BLOOD-PRESSURE

Date	Systolic	Diastolic
November 15.....	115	80
November 17.....	115	85
November 18.....	100	70
November 20.....	105	70
November 26.....	120	85

About two weeks before admission into the hospital the patient's blood-pressure taken in the out-patient department was 170-105.

URINE

Date	November 15	November 18
Transparency	Clear	Cloudy
Color	Straw	Straw
Reaction	Acid	Acid
Specific gravity.....	1020	1020
Albumin	+++	+++
Sugar	Negative	Negative
Casts	Hyalin and granular (many)	Hyalin and large and small (many)
Leukocytes and pus cells.	+++	A few
Red cells	++	A few

BLOOD

Date	November 15	November 18
Erythrocytes		
Leukocytes	7000	7600
Polymorphonuclears	72 per cent.	
Small lymphocytes.....	23 per cent.	
Large mononuclears.....	1 per cent.	
Eosinophils	4 per cent.	
Wassermann	Negative	

Functional Tests.—November 19, 1921—Phenolsulphonephthalein 0 in two hours. November 22, 1921 (intravenously) 0 in two hours. November 20, 1921, blood urea 139.65 mg. per 100 c.c. November 26, 1921, blood urea 208.05 mg. per 100 c.c.

Diagnosis.—Subacute diffuse glomerulonephritis (extra-capillary), nephrosis, pleurisy with effusion (left), and otitis media (left).

AUTOPSY REPORT.—T. J., negro, male. Well developed and well nourished; rigor mortis present, but easily broken up; slight frontal alopecia; subcutaneous ulcers on lower extremities from which grayish pus could be expressed; both legs increased in size, and pit on pressure; a small decubitus ulcer over sacrum.

Internal Examination.—*Lungs:* Left pleural sack full of straw-colored fluid; all lobes adherent to thoracic wall by fibrous adhesions, giving lungs a ragged appearance when removed; size about normal; substance engorged with fluid containing many fine bubbles and could be pressed together in hands. *Heart:* About normal size; pericardial fluid not increased in amount; lining smooth; valves intact; musculature firm. *Aorta:* A few patches of intimal thickening throughout length. *Liver:* About normal size; consistency firm; on section, diffuse yellowish brown; small stellate thickenings of capsule on anterior surface of the right lobe causing slight drawn appearance of liver substance; slight fibrous adhesions between under surface of right lobe and omentum. *Gall-bladder:* Negative. *Spleen:* Increased in size; capsule slightly roughened by

thickened patches of fibrous connective tissue; consistency firm. No bulging when sectioned; color, dark red. *Kidneys*: Considerably increased in size; capsule strips with ease leaving a smooth surface; yellowish, mottled color; several small cortical cysts, containing clear fluid; cortex, grayish yellow in color, considerably thickened, pyramidal portion dark red and well differentiated from cortex. *Suprarenals*: Normal. *Urinary Bladder*: Distended with urine and stringy mucus. *Penis*: Small stricture in anterior urethra. *Brain*: Appeared normal macroscopically.

Microscopic Examination of Kidney.—Glomeruli, not particularly enlarged, but some increase of cellular elements, leukocytes and endothelial cells. The capillary loops contain very little blood. The intracapsular space is filled with desquamated cells, fibrin and detritus forming in many the half-moon bodies. The epithelium of the proximal convoluted tubules show diffuse granular and fatty degeneration. The same process to a much less extent is seen in the straight tubules.

Anatomical Diagnosis.—(1) Subacute diffuse glomerulonephritis (extra-capillary); (2) nephrosis; (3) left serofibrinous pleuritis; (4) edema and multiple abscesses of lower extremities; and (5) inactive tuberculosis of lungs, liver, spleen and kidneys.

Chronic Diffuse Glomerulonephritis

(Second Stage)

As stated above, the separation of chronic diffuse glomerulonephritis into two stages is done on a functional basis. The second stage is represented by those cases in which there is little or no impairment of the function. It is realized that there is a transition from the second to the third stage, when at times differentiation is difficult, but those cases occupying either extreme of the series are readily recognized.

Etiology.—These cases undoubtedly arise from an acute glomerulonephritis, although the acute stage often passes unrecognized, especially if in the latter edema was absent or routine examination of the urine was not carried out. The etiology of the chronic form is the same as the acute, streptococcic infections play the chief rôle. It usually occurs in the early decades of life and is rare after the fiftieth year of age.

Symptomatology.—The mode of onset is variable. The patient may complain of no symptoms at all. It is frequently discovered in an examination for life insurance or in the course of an examination occasioned by complaints referred to some other trouble. Occasionally a recurring hematuria may be the symptom which brings the patient to the physician. More often the symptoms of the onset are general complaints such as headache, fatigue, tendency to dizziness and pain in the back. Sometimes an ever-recurring or never-disappearing edema may be complained of. This may be of renal or cardiac origin.

PHYSICAL EXAMINATION.—The condition of nutrition is usually below par, but often good. It never shows the cachexia of the third stage with marked insufficiency.

Blood-pressure.—This is increased. The systolic pressure is more frequently higher than that of the acute stage and lower than the third stage. It may show marked lability, not infrequently reaching normal values with rest in bed or as the result of intercurrent fever or heart weakness. However, on getting up and assuming the usual duties, with the subsidence of the fever, or with the restoration of the cardiac strength it tends to rise again. If the patient is seen for the first time when the pressure is within normal limits, the symptoms and the presence of slight cardiac hypertrophy will enable one to account for it.

Slight cardiac hypertrophy can almost always be demonstrated. It is, however, not so great as in the third stage. It tends to be greater with marked hypertension and the long existence of the nephritis. The left ventricle is more involved in the hypertrophy. As a result of beginning failure of the left ventricle not infrequently symptoms of relative myocardial insufficiency, such as shortness of breath on exercise, paroxysmal attacks of difficult breathing at night, or a feeling of constriction in the chest will be complained of by the patient. Very marked hypertrophy of the left ventricle is unusual unless some cause for the same accompanies the nephritis.

Edema.—Edema is not an essential sign of chronic diffuse glomerulonephritis. All stages of diffuse glomerulonephritis may run their courses without any edema at all. Not infrequently those cases which have shown edema in the acute stage will be free of edema in the chronic stage. There is often slight puffiness of the eyes and face. On the other hand, edema may be quite marked when it will usually be due to one of two causes or to both, *viz.*, an associated nephrosis or myocardial insufficiency.

Uremia.—The symptoms of true uremia or urinary poisoning never occur in the second stage of chronic diffuse glomerulonephritis. Volhard and Fahr state that eclamptic uremia rarely occurs. The author has observed it in 2 of his cases.

LABORATORY FINDINGS.—Urine.—The quantity usually corresponds to the fluid intake. The color is normal except in the recurring hemorrhagic form when it will have the appearance of blood. The reaction is acid. Albumin is present but varies very much in quantity. In uncomplicated cases it is usually small in amount, varying from a trace to 1 or 2 per cent. The quantity of albumin is not an indication of the severity of the nephritis. In cases associated with myocardial insufficiency it tends to be present in larger amounts. In cases associated with nephrosis the quantity is always quite large. Microscopically, except in the hemorrhagic form, a few red and white blood-cells are present. Casts of all kinds are found. Fatty epithelial cells are present in cases associated with nephrosis, but may also be present in cases without marked albuminuria and dropsy.

Blood.—Often a mild secondary anemia is present. In none of the author's cases have the red cells been lower than 3,000,000 per cm. In uncomplicated cases the total and differential leukocyte count is normal.

SPECIAL EXAMINATIONS.—Changes in the eye-grounds occur more

frequently than in the acute stage but less often than in the end stage of diffuse glomerulonephritis. In cases associated with arteriosclerosis the retinal vessels may be contracted and tortuous. True albuminuric retinitis may be present. One case reported by Volhard and Fahr showed choked disc.

FUNCTIONAL TESTS.—The characteristic feature of this stage is the absence of any marked impairment of the kidney function as shown by the usual tests. Still slight disturbances, such as a slight excess of the quantity of night urine as compared with the day, may be present. This is especially marked in the cases associated with myocardial insufficiency. According to Volhard and Fahr the water test—the time and amount of urine excretion after the administration of 1500 c.c. of water by mouth on a fasting stomach—shows good results, though the half-hour single quantities of urine tend to be less than in health.

The concentration test—the specific gravity of the urine excreted on a dry diet—is good. The specific gravity and salt and nitrogen excretion in uncomplicated cases vary but little from normal; but with nephrosis may vary as in that condition. With the presence of myocardial insufficiency the rather distinct characteristics of that condition are found. (See Nephropathies of Circulatory Origin.)

The phenolsulphonephthalein output and the blood urea are within normal limits in uncomplicated cases. Schlayer's methods, according to Volhard and Fahr, are of little value. The excretion of potassium iodid is usually within the normal time limit, but may be prolonged in cases with or without edema. The lactose excretion may be good, indeed is almost always so, although the increased blood-pressure would seem to indicate the presence of a vascular lesion.

Diagnosis.—The diagnostic features are:

- (1) It usually occurs in the early decades of life, rarely after the fiftieth year.
- (2) No symptoms at all may be complained of; a recurring hematuria may be the symptom which brings the patient to the physician; there may be general symptoms such as headache, fatigue, tendency to dizziness and pain in the back; finally an ever-recurring or a never-disappearing edema may be complained of which may be either of renal or cardiac origin.
- (3) The condition of nutrition is usually below par but often good; it never shows the cachexia of the end stage.
- (4) The blood-pressure is increased but may show marked lability.
- (5) The heart is moderately hypertrophied.
- (6) There is usually present a moderate degree of secondary anemia with pallor.
- (7) The urine usually shows a normal quantity and specific gravity, slight albuminuria, casts, and only a few red blood-cells except in the hemorrhagic form. In cases with marked dropsy it may show the characteristics of nephrosis or of the stasis kidney.
- (8) Eye-ground changes are more frequent than in the acute stage, but less frequent than in the end stage.

(9) The chief diagnostic feature is the absence of any marked impairment of the kidney function.

(10) Eclamptic uremia not infrequently occurs; in cases associated with atherosclerosis, eclamptic equivalents may be present; but true uremia does not occur.

Complications, Sequelæ and Association with Other Diseases.—Nephrosis is a frequent association. Myocardial insufficiency has been a frequent complication in the author's cases. Arteriosclerosis may be an associated disease or a complication. Among other complications may be mentioned pleurisy, meningitis and bronchopneumonia.

Clinical Varieties.—As stated in the symptomatology one may meet four groups of cases: (1) Those without symptoms and discovered accidentally; (2) the hemorrhagic form with recurring attacks of hematuria; (3) those with general symptoms such as headache, fatigue, tendency to dizziness and backache; and (4) those associated with edema.

Treatment.—Uncomplicated cases require no more than the institution of measures for the protection of the kidneys. **Rest in bed** is usually not necessary except in those cases associated with an acute exacerbation or in the hemorrhagic form. While ordinary duties may be continued, the **avoidance of great bodily and mental fatigue and exposure to wet and cold** should be strongly urged. It is desirable that the patient take a diet sufficient to maintain bodily nutrition. The **O'Hare nephritic diet sheet** may be supplied, and a daily score of 20 to 25, i.e., 80 to 100 grams of protein, allowed. The diet taken should be checked up at intervals by the physician to see that sufficient calories are taken to maintain the normal degree of nutrition. Cases associated with nephrosis or myocardial insufficiency should receive treatment appropriate for these conditions (*q.v.*).

Pathology.—The kidney of this stage was earlier designated as the **large white or large variegated kidney**. It is constantly enlarged, though the enlargement may be slight or considerable. Fahr has noted kidneys of this type weighing 250 grams (8 ounces). The capsule is not adherent. On section the parenchyma wells out. The outer surface is smooth and of a pale gray or grayish yellow to a brownish color. Small hemorrhagic points are almost always to be observed. The cortex resembles the outer surface as to color and the presence of small hemorrhagic foci. Yellowish specks and streaks besides opaque spots may stand out in the gray or grayish-yellow background. It is widened and sharply differentiated from the dark pyramids. The cut surface is moist and glistening, and the consistency is softer than normal though does not show the fragile softness of the acute stage.

The microscopical changes dominate the picture. While proliferative and exudative changes inside of the glomerular loops and in the intracapsular space are associated in all cases, these processes usually predominate in one or the other location to such an extent as to justify separation and description of an intracapillary and an extracapillary form. In the intracapillary form the glomeruli are markedly enlarged, often filling out the whole capsule. The glomerular loops contain very

little blood and often are quite devoid of red blood-cells. There is a marked cellular increase inside the loops. These cells are both of the leukocytic and endothelial type, though the latter are more numerous. Frequently adhesions and hyalinization of the loops are seen and not infrequently a whole Malpighian corpuscle may appear as a hyalin clump. In the capsular space desquamated epithelium, coagulated albumin, and red and white blood-cells may be seen here and there, though the space is usually empty, so far as it is not filled with the enlarged glomeruli or closed by the adherence of the two layers of the capsule.

The interstitial tissue is in some areas thickened and small cell infiltration is seen, though not to any great extent. The epithelium of the proximal convoluted tubules may contain double refracting substances which may also be seen accumulated in the interstitial tissue, giving rise to the opaque spots seen microscopically. Focal areas of granular degeneration chiefly of the epithelium of the proximal convoluted tubules belonging to the more severely diseased glomeruli may be seen but these changes are not diffuse except in the case of nephrosis. The blood-vessels in young individuals will usually be found intact but sometimes atherosclerotic changes may be present.

In the extracapillary form of chronic diffuse glomerulonephritis the glomeruli are not particularly enlarged, though the cellular elements inside the loops are increased. The loops are more completely empty of blood than in the intracapillary form. Often they are adherent and hyalinized. The chief feature of this form is the proliferation of the cellular lining of the parietal layer of the capsule. The proliferated cells are arranged concentrically and are more or less intimately attached to the parietal layer of the capsule. They form the so-called half-moon bodies which partially fill the intracapsular space and compress the glomeruli. Frequently organization processes are observed which convert the epithelial masses into concentric layered connective tissue in which spaces lined by a cellular layer occur. Leukocytes, blood and fibrin are also present in the intracapsular space. Sometimes these figures are separated from the wall of the capsule and form half-moon circular masses.

Granular and fatty degeneration of the tubular epithelium may be quite marked, but is not so diffuse as in the second stage of nephrosis. Blood and casts are present in the lumen of the tubules as described in the intracapillary form. In some cases the fibrin content is quite marked in the intracapsular space and inside the capillary loops. Various views have been advanced as to the significance of this fibrin. Engel regarded it as a primary inflammatory product. Löhlein considers it a secondary product of the extravasated blood. Fahr has observed that fibrin excretion is not a marked feature in the early stage of the inflammation and holds that in the course of glomerulonephritis fibrin is found on the inflamed layers of Bowman's capsule analogous to the fibrin formation in pleuritis and pericarditis.

Von Kaldeen has described a thrombosing form of glomerulo-

nephritis, characterized by a richness of fibrin in the capillary loops as well as in the vasa afferentia. Cardiac hypertrophy is usually present in chronic glomerulonephritis of the second stage, but does not reach a very high grade. According to Fahr, heart weights of from 400 to 500 grams (13 to 17 ounces) are observed. It is questionable whether kidneys which have reached this stage ever completely heal.

ILLUSTRATIVE CASE NO. I—Mrs. F. G. R., white, 45 years of age, married, housewife, seen at the author's office January 12, 1921.

Chief Complaint.—Dull headache, chilly sensations, occasional fever and general malaise.

Family History.—Father died of pneumonia; mother died of paralysis; seven sibs, three died in infancy, four are alive and well.

Past History.—Measles, pertussis, varicella in childhood. Since early adolescence she has had catarrhal trouble and her hearing has been impaired for several years.

Menstrual and Marital History.—Menstruation began at 16 years of age; is of the 28-day type; duration, 3 to 4 days. She has one child, 15 years of age. She has had no miscarriages. Menopause occurred at 41.

Present Illness.—About twelve years ago she had a prolonged spell of illness which was diagnosed malaria. She took quinin heroically and after some time she was relieved. Had no trouble for four or five years. For several months at intervals she has a general dull feeling, aching of the limbs and shoulders, chilly sensations followed by slight rise of temperature and loss of appetite. She has lost no weight. When she has these attacks she craves something cold and sour to drink. Since her attack 12 years ago she has been unable to take enough quinin because of catarrh and the condition of her ears. Symptoms referable to the circulatory system are negative. She has a slight hacking cough which is aggravated during these attacks. No symptoms referable to the gastro-intestinal system except anorexia. Urinary symptoms are negative. Her chief complaints are headaches and general malaise.

Physical Examination.—She is well-nourished lady. Temperature is 99° F. (37.22° C.). Pulse 120 per minute, blood-pressure 150-90. **Head and Neck:** Eyes, pupils are equal, regular, react to light and distance; movements are normal and show no signs referable to the autonomic nervous system except a positive Rosenbach. The eye-grounds are negative. **Ears:** The hearing is markedly impaired in both ears; there is no discharge. **Sinuses:** The paranasal sinuses illuminate well. **Throat:** Red, though the tonsils are of normal size and nothing can be expressed from them. **Teeth:** Apparently in good condition. The mucous membranes are of good color. The cerebral nerves are without abnormal findings. The neck is negative. **Chest:** Respiratory movements are full and equal on both sides and the lungs are negative. **Heart:** Point of maximal impulse in the fifth interspace, 10 cm. (4 in.) from the midsternal line, no enlargement to the right; the sounds are rather

accentuated, no murmurs. *Abdomen*: Abdominal findings are negative. *Reflexes*: Normal, there is no tremor. *Pelvic organs* not examined. *Urine* (Catheterized Specimen): Clear, light amber, acid, specific gravity, 1012, a trace of albumin, hyalin and granular casts, an occasional leukocyte and no red blood-cells. *Blood*: Differential count; polymorphinuclears, 50 per cent.; small lymphocytes, 46 per cent.; large mononuclears, 4 per cent.; red cells normal in shape, size and staining reaction; Wassermann is negative.

Functional Tests.—Phthalein injected intramuscularly shows 75 per cent. in two hours and ten minutes. *Blood Urea*: 34.5 mg. per 100 c.c. *Sputum*: Three specimens negative for tubercle bacilli. X-ray examination of chest does not show evidence of tuberculosis.

Diagnosis.—Clinical, chronic diffuse glomerulonephritis (intracapillary).

ILLUSTRATIVE CASE NO. II.—A. H., negro, female, age 40, housekeeper; admitted to the Memphis General Hospital March 13, 1921; discharged at her request March 29, 1921.

Chief Complaint.—Shortness of breath on exercise, swelling of the legs, pain in the scapular region.

Family History.—Father died of tuberculosis; she was not exposed; mother is alive and well; five sibs, all alive and well.

Past History.—In childhood, measles, pertussis and mumps. Since adolescence, chills and fever, influenza in 1919.

Menstrual and Marital History.—Menstruation began at 12 years of age, of the 28-day type; duration, 4 days; dysmenorrhea, in bed two days at onset; four children, normal deliveries, no miscarriages.

Present Illness.—Began with shortness of breath after attack of influenza in 1919; at this time she also had a cough which was non-productive until last November. She now expectorates large amounts of thin whitish sputum. Two months ago she began to have pains in the shoulders. These came on gradually, but are now lancinating and radiate down each side as far as the costal margin. The feet and legs have been swelling during the day for the past two weeks. The swelling disappears after a night's rest. Nocturia from 2 to 3 times. She has a feeling of constriction over precordial region. At times there is orthopnea. She also complains of anorexia, general weakness, insomnia, less of weight and constipation.

Physical Examination.—A fairly well-nourished and well-developed negro woman apparently 40 years of age. *Eyes*: Pupils are equal and react to light and distance; conjunctivæ are anemic. *Tongue, Throat and Tonsils*: Negative. *Teeth*: All missing except the six lower front which are in good condition. *Heart*: Apex beat diffuse and heaving; point of maximal impulse in the fifth interspace 11 cm. from the mid-sternal line; there is a systolic murmur at the apex, transmitted to the axilla: aortic second is accentuated; the pulse is of high tension and the radials are palpable. *Chest*: Normal in contour except for slight depression below the clavicles. Bronchovesicular breathing over the left apex, moist musical râles with impaired resonance and exaggerated voice and

tactile fremitus over upper left anteriorly. *Abdomen:* There is edema of the abdominal wall; the abdomen is distended, with a positive fluid wave; the liver and spleen are slightly enlarged and tender. *Extremities:* The skin is dry; scars over the left tibia; edema of the feet and legs. *Reflexes:* Present but sluggish. Sexual organs not examined.

Course.—She remained in hospital thirteen days without fever, the pulse ranging from 84 to 118 per minute. The edema had about disappeared, the systolic murmur persisted and upon her request she was discharged feeling better.

Blood-pressure.—March 17, systolic 200, diastolic, 140; March 21, systolic 195, diastolic 140.

Urine.—March 17, cloudy, straw-colored, specific gravity, 1020, acid, albumin + + +, hyalin and finely granular casts numerous, an occasional pus cell, no red blood-cells.

Functional Tests.—Phthalien (intravenously) 55 per cent. in two hours; blood urea, 18 mg. per 100 c.c.

Blood.—Red cells 3,000,000; leukocytes 9,300; polymorphonuclears 63 per cent.; small lymphocytes 20 per cent.; large mononuclears 15 per cent.; eosinophils 2 per cent.; Wassermann reaction negative.

Sputum.—Three examinations showed no tubercle bacilli.

X-ray.—Shows peribronchial thickening more marked in the left lung.

Clinical Diagnosis.—Chronic diffuse glomerulonephritis second stage (intracapillary), with myocardial insufficiency, and secondary anemia.

ILLUSTRATIVE CASE NO. III.—J. S., white, male, 46 years of age, laborer; admitted to the Memphis General Hospital, December 24, 1915; discharged, improved, April 3, 1916.

Chief Complaint.—Shortness of breath; general anasarca.

Family History.—Father died of Bright's disease at 72; mother is dead, cause unknown; four brothers are living, in good health; four brothers are dead, cause unknown. Three sisters are dead, one died in infancy, one from measles, cause of death of other one not known.

Past History.—Of childhood diseases he had only measles; pneumonia at 18, the attack lasted about nine days and he completely recovered; from May, 1915, to July, 1915, he had chills and fever; seven years ago he had sudden sharp pains in the back and hips; these were fleeting in character; he did not go to bed nor stop work on account of them; they continued at intervals over a period of five years, during which time he was a laborer in Indiana coal mines. Five years ago both hips were severely bruised, and right shoulder joint was dislocated. He was laid up 6 weeks; he denies any venereal disease; has had hemorrhoids, which protrude, itch and bleed since he was sixteen years of age.

Habits.—He drinks six cups of coffee; chews two twists of tobacco in three days; smokes occasionally; a whiskey or beer occasionally, and gets intoxicated about twice a year.

Present Illness.—Last October for a day and a half would pass about one teaspoonful of blood after urinating. About the first of

November began to have rigors every fourth night, which continued for two weeks. During these attacks had to urinate from 3 to 4 times at night. After two weeks the rigors at regular intervals ceased and would have only an occasional chill. At this time, about December 1st, his feet began to swell. He was passing as much urine by night as by day. These symptoms continued in somewhat increased severity up to admission in the hospital. At this time his face, feet, legs and scrotum were edematous, and he had shortness of breath.

Physical Examination.—Patient is well developed and nourished. **Eyes, Ears and Nose:** Normal. **Tongue:** Slightly coated. **Teeth:** Bad and there is marked pyorrhea. **Cervical Glands:** Not enlarged. **Heart:** The apex beat is in the sixth interspace 10 cm. from the midsternal line; it is strong and no thrills are palpable; there is no enlargement of cardiac area of dulness to the right. The sounds are clear, aortic second accented, no murmurs. **Lungs:** The breath sounds are normal and no signs of fluid in the pleural cavities. **Abdomen:** Is distended with gas and free fluid—flatness at the sides, movable, fluid wave, and tympany at the top; neither spleen nor liver is palpable. **Extremities:** Feet, legs and scrotum are edematous. **Urine:** Straw-colored, specific gravity 1020, albumin + + +, small and broad granular casts, an occasional leukocyte and no red blood-cells. **Blood-pressure:** 160–90. **Temperature:** 100° F. (37.77° C.). **Pulse:** 80 per minute.

Course.—The patient was very weak; there was a slight rise of temperature daily to December 30, 1915. The edema gradually disappeared with a markedly increased urinary output. On January 27, he had a chill with rise of temperature and malarial parasites (estivo-autumnal) in the blood. On March 1, 1916, he had an uremic convulsion. He was unconscious for forty-eight hours; after this he gradually improved. March 14, 1916, hemorrhagic retinitis both eyes, typical albuminuric spot in left eye and a beginning of one in the right eye. From about March 17, 1916, he gradually improved and was discharged from the hospital April 3, 1916.

URINE EXAMINATIONS

Date	Dec. 25, 1915	Dec. 28, 1915	Jan. 16, 1916	Jan. 29, 1916	Feb. 2, 1916	Mar. 8, 1916	Mar. 21, 1916	Mar. 31, 1916
Color	Straw	Light	Straw	Amber	Amber	Amber	Amber	Amber
Reaction	Alkaline	Acid	Acid	Acid	Alkaline
Specific Gravity ...	1020	1010	1015	1028	1022	1020	1020	1015
Albumin	++++	+++	++	++	++++	+++	++	+++
Casts	Many	Many	++	++	+++	++	++	++
Leukocytes and pus	+	+	+	+	Negative	+	Negative	Negative
Red Blood-cells ...	Negative	Negative	Negative	Negative	A few	Negative	Negative	Negative

BLOOD

Date	Feb. 29, 1916	March 13, 1916	March 25, 1916
Red cells.....
Leukocytes
Polymorphonuclears	56 per cent.	79 per cent.	78 per cent.
Small lymphocytes.....	18 per cent.	15 per cent.	16 per cent.
Large mononuclears.....	22 per cent.	6 per cent.	6 per cent.
Eosinophils	2 per cent.
Parasites	Estivo-autumnal
Wassermann	Negative, Dec. 28, 1915

BLOOD-PRESSURE

Date	Systolic	Diastolic
February 18, 1916.....	168	..
March 3, 1916.....	158	..
March 7, 1916.....	158	..
March 11, 1916.....	158	..
April 4, 1916.....	110	80

MOSENTHAL'S KIDNEY-TEST DIET

Date	Hour	Nitrogen		NaCl		Non-pro- tein N. in blood	Urine
		Per cent.	Grams	Per cent.	Grams		
Jan. 6-7, 1916	8 A. M.-8 P. M.	1.012	3.885	.88	3.38	25.1 mg. per 100 c c. 54 mg. per 100 c.c.	384 c.c.
Jan. 6-7, 1916	8 P. M.-8 A. M.	.62	3.98	.582	3.364		642 c.c.
Jan. 11, 1916	9 A. M.						
Feb. 17, 1916	3 P. M.						
Total		.767	7.865	.756	7.748	79.1	1026 c.c.

Clinical Diagnosis.—Malaria estivo-autumal, chronic diffuse glomerulonephritis (2nd stage), nephrosis, uremia (eclamptic), and albuminuric retinitis.

The End Stage of Chronic Diffuse Glomerulonephritis—The Chronic Form with Kidney Insufficiency, Including the Secondary Contracted Kidney

(Chronic Interstitial Nephritis; Secondary Chronic Interstitial Nephritis; Chronic Nephritis without Edema; Secondary Contracted Kidney; Small White Kidney)

This form of Bright's disease occurs more frequently than was formerly thought, due to the fact that many times it was mistaken for the primary contracted kidney since no history supposed to indicate chronic parenchymatous nephritis could be elicited. In the section on etiology attention was called to the fact as to how frequently the previous history in these cases showed the presence of focal infections with streptococci, such as tonsillitis, influenza-like diseases, otitis media, and sinus infection and as to how infrequently a previous history of scarlet fever was present. The great majority of these cases are the outcome of the second stage, but some may rise directly from the acute, especially from the severe extracapillary forms.

Symptomatology.—The mode of onset will, naturally, often be similar to that of the chronic diffuse glomerulonephritis without kidney insufficiency, that is, the disease may for a long time be latent, often exist for many years, when the first subjective symptoms to occur may be those of uremia, or it may be discovered accidentally, the only symptoms indicating kidney insufficiency being nycturia and polyuria.

The tendency to recurrences seen in the second stage is less frequent, though occasionally slight exacerbations with hematuria may occur. The great number of cases are characterized by chronic or periodical general symptoms. Many of these are due to the toxemia resulting from the kidney insufficiency. Among these symptoms most prominent are headaches, dizziness, scotomata, general weakness, fatigability, general nervous symptoms and insomnia. These may disable the patient temporarily and be followed by a period of freedom, which is in turn followed by a return of the symptoms. This periodicity may exist for many years before a fatal outcome; on the other hand, the symptoms may set in first a short time before the end.

Abdominal pain is a symptom not infrequently complained of by the patients; it may possibly be of the nature of an abdominal angina. Stengel and his co-workers have called attention to the frequency with which chronic nephritics complain of abdominal pain.

Symptoms referable to the heart are quite frequently present. These may be those of relative myocardial insufficiency, such as shortness of breath on exercise, periodical attacks of nocturnal asthma, palpitation, etc., or those of complete cardiac decompensation. The latter are as a rule likely to be associated with the outbreak of uremia, when both are due to the impaired ability of the kidney to excrete water.

UREMIA.—True uremia, that form associated with the retention of the end products of nitrogen metabolism is the inevitable outcome if life is sufficiently prolonged.

The symptoms vary in degree and resemble those associated with suppression of urine. Dyspeptic symptoms are anorexia, which may increase to unwillingness on the part of the patient to take anything by mouth, nausea, periodic or constant vomiting, associated with great general weakness and exhaustion. As a result of the polyuria which produces a great drain on the fluids of the tissue, thirst is quite frequently complained of. There may be present dryness and inflammation of the mucous membranes of the mouth and nose associated with macerating hemorrhages. Feter urinosus ex ore is rarely absent. Hiccup and itching of the skin often increase the nervous irritability already present. There is inability to sleep soundly. The patient often takes short naps from which he wakes with a start. Associated with the nervous irritability fibrillary twitching of the muscles and tendons is often to be observed. Pain over the precordium and side of the chest may be complained of—the result of the pericarditis or pleuritis which is often a manifestation of uremia. These symptoms are not developed in their entirety in every case.

Dyspeptic complaints associated with great weakness may stand in the foreground a long time before the patient with increasing somnolence passes into complete coma. On the other hand, the symptoms may set in with the suddenness of a catastrophe. Eclamptic uremia rarely occurs in these cases. Volhard has observed convulsions in only 5 cases. In one case, these occurred after an infusion of sodium chlorid glucose solution; in a second, after added salt in testing kidney function; in two other cases of subchronic extracapillary nephritis in which death resulted one half and one year, respectively, after the acute nephritis; and in the fifth case a large subdural hematoma was present. Pseudo-uremic symptoms, so-called eclamptic equivalents, may occur in cases associated with arteriosclerosis of the brain, heart and peripheral vessels. At times during fatal uremia, angina pectoris, cardiac dilatation, Cheyne-Stokes' breathing and symptoms referable to the cerebral and peripheral vessels may occur. All of these as well as the symptoms of cerebral hemorrhage and softening are much less frequently encountered than in benign hypertension and this combined with glomerular lesions—the combination form.

PHYSICAL FINDINGS.—In the early stages, the general appearance of the patient may be scarcely altered. With the progress of the disease there is a gradual loss of strength and towards the end a characteristic cachectic appearance is present. The panniculus is scant, the muscles are flaccid and there is marked pallor, a grayish yellow or a yellowish brown color of the skin. The eyeballs frequently protrude, giving the patient the appearance of one suffering from Basedow's disease. The skin is dry as is also the hair, which is brittle and tends to fall out. Occasionally subcutaneous hemorrhages are observed. Hemorrhages beneath and from the mucous membranes also occur. The eyes may be bloodshot. Epistaxis, menorrhagia and hemoptysis may be present.

Blood-pressure.—Increased blood-pressure is an essential finding. It tends to be higher and more constantly maintained than in the first and

second stages. Readings as low as 160 to 170 systolic are rare. In 37 cases, Volhard and Fahr report values over 200 in 14 cases and in one case a systolic pressure of 272 was present. The hypertension tends to be more constant and greater the longer the nephritis has existed. In the early stages or less severe cases it may vary as in the second stage, and under conditions, such as great cardiac and general weakness, may reach normal values for a long or shorter time.

There are probably several factors which contribute to the high and persistent increased blood-pressure in this form of nephritis:

(1) With extensive destruction of the kidney filter a permanent increased blood-pressure sets in probably reflexly by contraction of the peripheral vessels (Aschoff).

(2) Hypertension may arise in connection with unknown intoxication which causes disturbance of the central nervous system which we call uremia. This intoxication is not one of retention in the strict sense, though it is most commonly present in those cases of advanced nephritis which manifest marked nitrogen retention. Clinically, it is associated with severe acute nephritis, sometimes at its very onset, besides the sub-acute and chronic inflammatory affections of the kidney (Janeway).

(3) Not infrequently atherosclerosis of the small vessels of the kidneys is present in the end stage of chronic nephritis. Some have attributed these changes to the hypertension of glomerulonephritis. Fahr argues that if this were so, one would expect to find similar changes in the arterioles of other areas which are subjected to the same pressure. Atherosclerotic changes may occur in the kidney vessels and be entirely absent in other organs in these cases. Therefore the increased blood-pressure, while it may assist, cannot be the essential cause of the atherosclerosis. This cause must arise in the kidney itself and is chiefly of a mechanical nature. Fahr summarizes his views on this question in the following way: In glomerulonephritis, especially in its chronic form, strong functional demands are made upon the vascular system of the kidney in consequence of the disease of the glomeruli accompanied by progressive destruction of the same. This strong demand is the cause of the atherosclerotic process in the vessels, and the atherosclerosis of the vessels of the kidney produces an increased blood-pressure which is superimposed on the primary hypertension produced by the glomerular disease. The more marked the vascular changes are the more will the degree of hypertension and cardiac hypertrophy approach the conditions in the combination form (the genuine contracted kidney).

The Heart.—While there may be a few exceptions, the heart is regularly enlarged in the end stage of chronic diffuse glomerulonephritis. The left ventricle is always primarily involved, though hypertrophy and dilatation of the right heart is not infrequently associated with the left-sided hypertrophy. The degree of the cardiac hypertrophy rarely reaches that seen in benign hypertension and the combination forms. Jores and others have called attention to the difference which exists between the cardiac hypertrophy in the primary contracted kidney—the red granular kidney—and the secondary contracted kidney. The

apex beat is usually pronouncedly heaving and felt in or outside the midclavicular line. There is frequently a presystolic gallop rhythm and in cases associated with involvement of the right side of the heart, a systolic or presystolic venous pulse, widening of the cardiac area to the right, the systolic murmur of relative mitral insufficiency, enlargement of the liver, transudates into the serous cavities and edema are to be made out. Arrhythmias are not frequent. The orthodiagraphic measurements are increased; on an average median right equals 5.3 cm.; median left equals 10.4 cm.; and longitudinal equals 17.2 cm. The electrocardiographic tracings almost constantly show left-sided preponderance.

The cardiac hypertrophy is probably dependent upon the hypertension, which as we have seen depends upon several factors. Besides the hypertension associated with glomerular destruction, an important rôle is attributed to the vascular changes developing in the course of glomerular nephritis. Fahr was unable to establish an exact parallelism between the intensity of the vascular changes and the degree of cardiac hypertrophy; however, the latter as a rule was greater in those cases in which marked changes in the small kidney vessels was present. Thus in 5 cases in which the total heart weight exceeded 600 grams (9259.38 grains); in 3 marked, and in 2 very marked vascular changes were present. In 9 cases in which the total heart weight was less than 600 grams, only 3 showed marked vascular changes, in 4, vascular changes were present but in variable degree, and in 2, they were slight. Jores has shown that the degree of tissue destruction in the kidney cannot be the decisive factor in the origin of the cardiac hypertrophy.

The accessible arteries are frequently palpable. Marchand has called attention to chronic nephritis as a cause of arteriosclerosis in early life. Views vary greatly as to the importance of mechanical influence, the result of the hypertension and the toxic influence, the result of kidney insufficiency in the production of arteriosclerotic changes in the large blood-vessels. Volhard calls attention to the fact that arteriosclerotic changes in the large blood-vessels are often more pronounced in the end stage of chronic glomerulonephritis than in benign hypertension which would indicate the relatively greater importance of toxic influence.

Edema.—Edema here as in other types of glomerular nephritis is not an essential symptom. Even in cases where the previous history has shown the presence of edema due to an associated nephrosis edema may be present; although nephrosis which manifests itself clinically by the presence of edema may complicate the end stage of chronic glomerulonephritis.

Edema of cardiac origin is quite frequently present and is sometimes difficult to differentiate from renal edema. Enlargement of the liver and increased venous pressure determined by the method of Hooker and Eyster or A. A. Howell, give conclusive evidence for the cardiac nature of the edema.

LABORATORY FINDINGS.—*Urine.*—There is regularly a polyuria in these cases. The color is light yellow often clouded by the presence of organ-

ized sediment. The reaction is acid. Albumin is usually present in small amount. Microscopically, are to be seen hyalin and granular casts in varying numbers, fatty epithelium and detritus.

The above urinary findings are changed by a complicating myocardial insufficiency or nephrosis when they may assume the characteristics described for these conditions.

Blood.—Secondary anemia is regularly present; it varies greatly in degree, but may be quite marked.

SPECIAL EXAMINATIONS.—*Kidney Functional Tests.*—Impairment of kidney function is the feature which distinguishes this stage from that of the second stage. The degree of functional incapacity varies greatly and there are naturally all stages, from the slight to the severest degrees. One of the first manifestations of insufficiency is a night polyuria (600 c.c. or more) with a low specific gravity. Another early indication of insufficiency is an inability of the kidney to concentrate. This is shown in the fixation of the specific gravity around 1012 in the single portions of urine passed at two-hour intervals during the day; and also in the low specific gravity of the urine while the patient is on a dry diet. In cases not associated with edema the water test usually results poorly.

While the total daily excretion of sodium chlorid may reach the normal quantity on account of the polyuria present, the impairment of salt excretion is shown by the low percentage excretion and by the fact that added portions of salt are excreted over a much prolonged period and may be completely retained. Nitrogen retention is almost as constant as the tendency to a fixation of the specific gravity and a night polyuria. It is not possible, sometimes, to obtain from careful metabolic determinations as to nitrogen intake and output an idea of the nitrogen retained, as a result of the impaired kidney function. In this the quantitative excretion of nitrogen may be sufficient, *i.e.*, may correspond to the intake and yet the kidneys may suffer greatly in this important function, as shown by adding known quantities of urea to the diet which will be excreted only after a prolonged period, and by quantitating the non-protein nitrogen or urea in the blood, which in cases of this group is usually decidedly increased. The author has ordinarily regarded, according to McLean, urea values of 50 mg. per 100 c.c. of blood as high normal. The degree of increase, however, varies greatly, being dependent upon the protein intake and the degree of kidney insufficiency. The other components of the non-protein nitrogen are also found to be above normal.

Lactose excretion is regularly prolonged as is also that of potassium iodid. However, according to Volhard and Fahr these tests are of doubtful value as to diagnosis and prognosis in these cases.

Ophthalmoscopic Examination.—As a rule the eye-grounds show changes. Albuminuric retinitis is quite frequent, though only small hemorrhages and plaques may be present.

Basal Metabolism.—The basal metabolic rate varies. According to Mosenthal and Marks, in some cases associated with marked dyspnea the metabolism rises as high as 50 per cent. above the average. The

dyspnea is the factor that produces this change. A rise in blood-pressure, the presence of an acidosis or the existence of even marked impairment of renal function, as measured by conventional tests, does not influence the plane at which metabolism proceeds. The abnormally high metabolic rates occurring in certain nephritics has been attributed to dyspnea and restlessness characteristic of the severe types of the malady; previous fasting and undernutrition may be responsible for some of the low figures presented.

Furthermore, a study of the respiratory quotient makes it evident that the metabolism of proteins, fats and carbohydrates is in nowise disturbed in cases of heart and kidney disease thus far observed in the calorimeter.

Acidosis.—Some acidosis is usually present in these cases as shown by Sellard's test (it requires more than 5 to 10 grams [77.16 to 154.32 grains] of sodium bicarbonate administered by mouth to render the urine alkaline), by the alkali reserve of the blood (Marriott), and by the tension of the carbon dioxide of the alveolar air. Experimentally, MacNider has found that in acute tubular nephropathies there is a disturbance in the acid base equilibrium in the blood, determined by these methods, which precedes evidence of impaired function. With the following chronic nephropathy in some cases consisting in regeneration of the tubular epithelium of a flat, less specialized type and of the production of chronic obliterative and sclerotic changes in the glomeruli, the alkali reserve increases with improvement of kidney function as far as the elimination of phenolsulphonephthalein and the retention of blood urea and creatinin are concerned. Also in dogs with naturally acquired nephropathy consisting of injury of the glomeruli with well-preserved tubular epithelium, the alkali reserve of the blood may be normal with good kidney function. When such animals had an acute tubular nephropathy superimposed on the glomerular disease by the administration of uranium or mercuric chlorid, there was a rapid depletion of the alkali reserve of the blood and an associated decrease in the carbon dioxide tension of the alveolar air. From this it is inferred that the functional capacity of the renal epithelium has more influence on the acid-base equilibrium of the blood than disease of the glomeruli.

In the human tubular nephropathies (nephrosis), we have found neither the alkali reserve of the blood nor the carbon dioxide tension of the alveolar air reduced to any appreciable extent, while in the end stage of chronic glomerulonephritis there may be marked reduction in the alkali reserves (Marriott's method) and in the tension of the carbon dioxide of the alveolar air leading clinically to air hunger. This acidosis is generally regarded as a retention acidosis and often runs parallel with the impaired renal function as expressed by the phenolsulphonephthalein output and the retention of blood urea and creatinin.

Diagnostic Features.—(1) It usually occurs before the fourth decade.

(2) Symptoms may be absent until just before the end; there is not the tendency to recidives or acute exacerbations of the second stage;

edema of cardiac origin is quite frequent, but that of renal origin is rarely present.

(3) There is a constantly maintained high blood-pressure, usually higher than in other forms of nephritis, but under certain conditions exceptions may occur.

(4) The heart shows marked hypertrophy, but is not usually as great as in the atherosclerosis. It is frequently associated with dilatation and the symptoms of cardiac decompensation.

(5) The blood shows marked secondary anemia.

(6) The urine shows polyuria, hyposthenuria, slight albuminuria and cylindruria.

(7) Papillitis and neuroretinitis are the rule.

(8) The chief characteristic of this stage is the impairment of kidney function. There is a day and night polyuria. The two hourly day specimens show a fixed specific gravity around 1012; the night urine, a low specific gravity; there is impairment of the ability of the kidney to excrete water, salt and nitrogen; the phenolphthalein excretion is low, and there is marked retention of nitrogen as shown in the high blood urea and creatinin.

(9) There is true uremia, contracted pupils, digestive disturbances, hyperirritability, and hypersensitiveness of the body musculature with twitching of the same; urinous odor of the breath; dyspnea and hyperapnea, and frequently inflammation of the serous membranes, especially of the pericardium; fall of temperature; apathy; and stupor. Coma is the inevitable end if the patient lives long enough.

Complications, sequelæ, association with other disease and clinical types, have been mentioned in the description of the symptomatology, physical findings, etc., and need not be repeated here.

Treatment.—The prophylaxis of the end stage of chronic diffuse glomerulonephritis is that of the prophylaxis of nephritis in general. The realization that most frequently the end stage is the further development of the first and second stages emphasizes the importance of the early recognition of acute diffuse glomerulonephritis and its proper treatment in the prevention of the chronic stage with impaired function. While the findings of chronic foci of infection in any part of the body and their successful treatment can scarcely be expected to remove injury already done to the kidney, we may confidently expect such procedures to check the progress of the inflammatory process in the kidney, which by regenerative processes may maintain or materially improve an already seriously impaired function.

Such foci of infection may and should be judiciously removed. The author says judiciously, because such procedures undertaken without every safeguard may sometimes precipitate a fatal uremia.

The care of the patients in this stage of nephritis is largely a special problem, depending upon the condition present. In many cases with only slight impairment of functional capacity, the general measures will be those already described for chronic diffuse glomerulonephritis of the second stage. However, the latent cases which present no gen-

eral symptoms and only nycturia and hyposthenuria as manifestation of impaired function should receive careful attention as to the regulation of the patient's life with reference to rest, occupation, hydrotherapy, diet, etc. In these cases confinement to the house or bed is not desirable, nor should occupation be entirely given up. However, both **physical and mental strain** should be carefully **avoided**. An occupation which favors mild, pleasant outdoor exercise is desirable. An **occasional vacation**, favoring relaxation and rest, is to be urged. It may not be necessary for these patients to make a change of climate if this entails hardships in breaking up home ties, but residence in a **warm, equable climate** is an advantage. These patients do not usually do so well in the extremes of altitude—a moderate altitude in places where great extremes of temperature and moisture do not occur is more desirable. If these favorable conditions cannot be taken advantage of, especial protection against the disadvantages which environment imposes should receive great care. Remaining in the house as much as possible during cold damp weather, and, when it is necessary to go out, protection by proper clothing should be impressed on the patient. **Warm baths** are to be recommended; cold baths are contraindicated. The protein content of the diet should be regulated according to the condition of the kidney function as shown in the blood urea, but equal care should be exercised to see that the diet contains sufficient proteins to prevent catabolism of the body's own proteins, and other foods to furnish sufficient caloric value and balance. (See *Treatment of Second Stage Chronic Diffuse Glomerulonephritis*.)

Cases with acute exacerbations which do not occur so often as in the second stage should be treated as severe cases of acute diffuse glomerulonephritis.

The greater number of these cases will present general symptoms and more marked kidney insufficiency, and should be subjected to periods of **rest in bed** with careful regulation of diet and symptomatic treatment. The protein, salt, and fluids should be restricted, unless uremia threatens, in which case the fluids should rather be increased.

For short periods the proteins may be markedly restricted—30 to 40 grams (462.96 to 617.28 grams) or less per day; no extra salt should be added to food after it has been prepared and it should be used very sparingly in the preparation; the fluids should not exceed 1500 c.c. (3.2 pints) per day.

Those cases associated with edema should be treated according to the causative condition—myocardial insufficiency or nephrosis. The same principles and measures described under Nephrosis and the Stasis Kidney should be instituted. Myocardial insufficiency with threatened uremia should receive very active treatment, and the management of uremia is the same as that described there.

Other complications should be carefully watched for and proper treatment for them carried out.

Prognosis.—The prognosis in the end stage of chronic diffuse glomerulonephritis is ultimately bad. It is an incurable disease, but not

incompatible with many years of life. Death is most likely to occur from terminal infection, myocardial insufficiency and uremia.

The tests for kidney function may offer valuable information for prognosis (see *Uremia*). It must, however, not be forgotten that these tests may sometimes result poorly from extrarenal factors; *e.g.*, indiscretion in diet, acute exacerbation, or the supervention of myocardial insufficiency. Albuminuric retinitis is of bad prognostic omen in these cases.

Pathology.—It has already been emphasized that there may be great difference in the macroscopical appearance of the kidneys in chronic diffuse glomerulonephritis, and that the function may be markedly impaired in large smooth kidneys as well as in small contracted kidneys. In general, however, the kidneys in these cases may be divided in two groups:

(1) CHRONIC DIFFUSE GLOMERULONEPHRITIS WITHOUT GRANULATION.

—**Macroscopical.**—The size is diminished, though it need not be considerable; the capsule is usually adherent; the outer surface is perfectly smooth; the consistency is firm; the color is gray or slightly yellowish; no hemorrhages are visible; on cut surface, the medulla is brownish as compared with the cortex but relatively may be said to be pale; there is no sharp contrast between the medulla and cortex; the markings of the cortex are obscured.

Microscopical.—The *glomeruli* are uniformly involved, and it may frequently be determined whether the intracapillary or extracapillary process had previously predominated. Many are hyalinized as the result of the intracapillary process.

Often a portion of the glomeruli is changed to hyalin masses, while frequently the glomerulus is completely destroyed. Others are nearly destroyed, and the greater number of loops are completely empty of red blood-cells. Only a few show blood containing loops in large numbers and many of them lie at the periphery while the inner loops show hyalin degeneration. In the Malpighian corpuscles there is occasionally hemorrhage into Bowman's capsule. Usually, however, the capsular space is free—especially no epithelial desquamation. The *interstitial* tissue shows diffuse development of connective tissue between the changed glomeruli; that of the medulla is also increased. Fat and double refracting lipoids are present. The *tubules* are destroyed in great numbers; the preserved tubules are usually widened and contain numerous hyalin and granular casts, and occasionally red blood-cells. There is usually no distinct island formation, and granular degeneration is scarcely demonstrable in the epithelium.

The Blood-vessels.—The small blood-vessels show hypertrophic intimal thickening and arteriosclerosis. Changes may be present in the arciform and interlobular arteries but become slight or wholly disappear in the branches of the interlobular vessels. The feature of this form is the uniform involvement of the glomeruli which accounts for the smoothness of the outer surface. This form is much rarer than the following:

(2) **CHRONIC GLOMERULONEPHRITIS WITH GRANULATION.**—The chief characteristics of this form are (1) that a number of the glomeruli are preserved, (2) regenerative processes occur, and (3) the morbid processes do not usually come to a standstill, but if they do, they flare up on the slightest provocation until finally complete insufficiency leading to death occurs. The clinical history is necessary to determine whether the end stage has developed directly from the first stage or through the second stage. This form usually develops from the large white or variegated kidney.

Macroscopical.—The size varies. The kidney may still be large, but it is to be remembered that the size of the kidney is not necessarily an indication of how much of the parenchyma has been destroyed. The consistency is much firmer than that of the second stage. The capsule is more or less firmly adherent. The outer surface is granular, usually finely; the gray color predominates in the outer surface and in the cortex, but in the latter a brownish flecking may still be very pronounced. Small pin point hemorrhages may often be seen. On cut surface, the limit between the medulla and cortex is never so sharp as in the second stage, but may be distinct. From this small pale granular kidney the brownish red (secondary contracted) kidney finally develops. In this latter the granulations are usually tolerably equal in size, but marked depressions with large elevations may exist. The capsule is thickened and may or may not be adherent. The pyramids are often markedly contracted, but usually they merge into each other. The consistency is tough.

Microscopical.—The picture is quite variable in contrast to that of the chronic nephritis without granulation, due to the destruction of the parenchyma associated with regeneration.

Completely destroyed and severely injured glomeruli are seen along with others whose loops are fairly well filled with blood. In the advanced stage it is more difficult to recognize the intracapillary and extracapillary processes, though desquamated epithelium may be seen in the intracapsular space. Remains of the half-moon structures are evident. Net form strands may extend between the glomeruli and the parietal layer of the capsule. In other areas the glomeruli are changed into hyalin clumps surrounded by a border of intensively stained cells. In still other areas the glomeruli may consist of scantily filled loops, others again are plump and changed into homogeneous masses, which do not present the glassy appearance of hyalin.

These masses are poor in nuclei, although some may contain numerous nuclei of the endothelial type. There are also numerous completely destroyed glomeruli which are difficult to distinguish from the surrounding lesion. Some glomeruli may contain stiff permeable loops and some may be well filled with blood.

The tubules are widened, many grouped in island formation. These regenerated loops form the granules or nodules on the outer surface. The epithelium of the tubules occasionally show granular degeneration, though less than in the second stage. Fatty degeneration may be in evi-

dence. The degeneration of the tubules is probably largely due to the destruction of the glomeruli to which they belong, but there is evidence that this may in part be due to the direct action of toxins. This process is, however, never so marked or diffuse as in nephrosis. *The connective tissue* is much less uniform than in the second stage. There are quite marked changes in the *blood-vessels*—hyperplastic intimal thickening as well as regressive changes.

How this is brought about is a debated question. There is regularly hypertrophy of the heart, but this does not reach the extent which is seen in the primary contracted kidney. Fahr summarizes his views on these questions in the following way: In glomerulonephritis, especially in the chronic form, the vascular system is under marked strain as a result of the glomerular change accompanied by progressive destruction; this marked strain is the cause of the atherosclerosis of the kidney vessels and the atherosclerosis of the kidney vessels produces an increase of blood-pressure which is added to the primary hypertension produced by the glomerular changes.

ILLUSTRATIVE CASE NO. I.—C. P., colored, female, age 26, no occupation. Admitted to Memphis General Hospital September 10, 1919. Discharged November 4, 1920.

Chief Complaint.—Shortness of breath, swelling of feet and legs, anorexia, matutinal vomiting, pain in the lower abdomen, pollakiuria and nycturia.

Family History.—Father and mother dead, cause unknown; 5 sibs, 1 alive and well, 4 dead, cause unknown; no cancer, tuberculosis, syphilis or nervous disease in family.

Past History.—Has had the usual diseases of childhood; a leukorrheal discharge for about one month.

Menstrual History.—Began at 14; has always been regular, of 28-day type, duration from 3 to 4 days.

Present Illness.—Began three months ago with shortness of breath on exercise. She noticed swelling of the feet and legs two months ago; during this time she has had a poor appetite, attacks of vomiting in the morning and pain in the lower abdomen. The patient states that she has had to urinate every 20 or 30 minutes.

Physical Examination on Admission.—Well-nourished and developed female. Facies shows anxious, distressed expression; fairly marked dyspnea; conjunctivæ pale; tongue, central grayish coating, margins furrowed; moderate edema of the face, especially of the eyelids; notable pallor of oral mucous membranes; teeth in good condition, moderate retraction of gums; pupils react to light. **Thorax:** Expansion poor, respiration largely of abdominal type; apex impulse felt most distinctly in the sixth interspace 2.5 cm. (1 in.) outside the midclavicular line; to the right the area of cardiac dullness extends 2 cm. to the right of the right sternal margin and to the left to the anterior axillary line; there is marked accentuation of both aortic and pulmonic second sounds; there is a gallop rhythm; no murmurs are heard. The liver is apparently

within normal limits, the spleen is not felt, there is no sign of free fluid in the abdominal cavity. There is edema of the lower extremities. Temperature 99° F. (37.22° C.). Pulse 102. Blood pressure 175-130.

Urine.—Clear, straw-colored, specific gravity, 1007; reaction neutral. Albumin +; hyalin and granular casts + +; pus cells +. Blood, secondary anemia with slight leukocytosis.

Course.—September 13, 1919, patient had two convulsions—one at 2 P. M. and one at 9:15 P. M. They lasted two or three minutes and patient was in a semi-comatose condition for about 15 minutes following each convulsion. During convulsion pupils were slightly dilated and reacted to light, the breathing was stertorous, there was foaming at the mouth from which some blood exuded, probably due to biting tongue; the patient's attention could be attracted by calling her name, but she would not answer questions.

September 14, 1919, patient had three convulsions to-day.

September 25, 1919, patient's condition has improved considerably the last few days; edema has largely disappeared. She complains of no discomfort except nausea due to taking milk. The heart shows gallop rhythm, aortic second sharply accentuated, bell-like quality; lungs are negative.

September 26, 1919, patient feels better; swelling in feet has almost disappeared.

October 1, 1919, patient is in a stuporous condition, breathing heavily.

October 9, 1919, patient sleeps most of the time during the day.

October 14, 1919, patient complains of pain over precordium, her general condition is growing worse, is stuporous, there is a pericardial friction rub and gallop rhythm.

October 15, 1919, over the entire precordium, there is a pericardial friction rub.

October 16, 1919, patient complains of pain over precordium.

October 17, 1919, feet and legs are more edematous, dyspnea increased.

October 18, 1919, patient complains of pains in the legs and much dyspnea.

October 22, 1919, patient not so well; complains of pains in the epigastrium.

October 27, 1919, pericardial friction now much more pronounced, general edema is more marked, especially in the thighs; patient complains of pain in the right side; she seems very uncomfortable.

October 28, 1919, gallop rhythm, arrhythmia and pericardial friction rub very pronounced; edema of extremities more marked; patient is stuporous.

October 29, 1919, patient complains of pains over precordium; asthenia very marked.

October 31, 1919, patient is much worse; semi-delirious; respiration Cheyne-Stokes; pulmonic second sound weak.

November 3, 1919, nose bleeds very much, several times a day; incontinence of feces and urine; patient died at 9:15 P. M.; autopsy refused. The temperature was at no time above normal and distinctly subnormal from October 6 to time of death. The pulse varied from 88 to 124 per minute.

BLOOD-PRESSURE

Date	Systolic	Diastolic
September 10, 1919.....	175	130
October 6, 1919.....	180	135
October 7, 1919.....	195	150
October 14, 1919.....	150	120
October 15, 1919.....	160	120
October 17, 1919.....	198	165
October 21, 1919.....	160	120
October 24, 1919.....	168	125
October 28, 1919.....	148	120
October 31, 1919.....	155	155

Functional Kidney Tests.—September 27, 1919, phenolsulphonephthalein in 2 hours, 10 min., 0; October 22, 1919, phenolsulphonephthalein in 2 hrs., 10 min., 0; and October 2, 1919, two-hour specimens of urine show fixation of specific gravity at 1010.

Blood Urea.—September 28, 1919, 262 mg. per 100 c.c. of blood; October 6, 1919, 173.4 mg. per 100 c.c. of blood; and, October 24, 1919, 265.9 mg. per 100 c.c. of blood.

Creatinin.—October 6, 1919, 17.6 mg. per 100 c.c. of blood.

Ophthalmoscopic Examination.—Both fundi show neuroretinitis.

Clinical Diagnosis.—Chronic glomerulonephritis (end stage), myocardial insufficiency, double neuroretinitis, and uremia.

ILLUSTRATIVE CASE No. II.—A. F., male, negro, age 38, concrete worker; admitted to Memphis General Hospital October 7, 1920; discharged improved, October 26, 1920.

Chief Complaint.—Shortness of breath on exercise, and swelling of feet and legs.

Family History.—Father has rheumatism, right shoulder; otherwise negative.

Past History.—In childhood, measles and pertussis. Post-childhood, malaria, influenza-pneumonia twice, last attack two years ago. Tripper two years ago. Sore on penis 17 years ago. Never had an eruption; says his Wassermann taken at Outpatient Department was negative.

Present Illness.—He has not been well since his attack of influenzal pneumonia two years ago. Three weeks ago he noticed that his feet were swollen. This is worse toward night after he has been on his feet all day. He has headache, precordial pain and dyspnea. He has been gaining some weight in the last week but is weak and does not feel well. He has been spitting up blood at times for the past two weeks.

Physical Examination.—Male, black, well-nourished, 38 years of age. Temperature 98.4° F. (36.88° C.); pulse 84; blood-pressure 220-158 mm.

Hg. Seems comfortable. Eyes, tongue and throat negative; mucous membranes, a little pale. **Heart:** Slightly enlarged to the left; a soft systolic murmur at apex, transmitted toward axilla, not heard in the back; aortic second accentuated; reduplication of pulmonic second; radials palpable; pulse 100 per minute, full and bounding. **Lungs:** Slight dulness beneath the right clavicle; breath sounds diminished to some extent at right apex anteriorly; a few crackling râles heard at right apex and over the left base posteriorly; voice sounds diminished over left lobe posteriorly; other organs without abnormal findings; slight edema of both ankles. **Urine:** Clear, light yellow; specific gravity, 1009, reaction acid; albumin +; sugar, negative; casts + + + (hyalin, fine and coarsely granular); red blood-cells and pus cells negative.

Blood.—Leukocytes, 5,500; polymorphonuclears 74 per cent.; small lymphocytes 15 per cent.; large mononuclears 10 per cent.; eosinophils 1 per cent.; Wassermann, negative.

Functional Tests.—Phenolsulphonephthalein (intravenously), 15 per cent. in two hours.

Blood Urea.—119.4 mg. per 100 c.c.

Diagnosis Clinical.—Chronic diffuse glomerulonephritis (end stage), and myocardial insufficiency.

ILLUSTRATIVE CASE NO. III.—R. H., male, negro; age 25, works in cotton shed. Admitted December 9, 1920; died December 12, 1920.

Chief Complaints.—Bleeding from rectum.

Family History.—Father dead, rheumatism; mother, dead, pneumonia.

Past History.—Measles, mumps in childhood; Tripper in June, 1920. Has had nosebleed before, which lasted two days.

Present Illness.—A few days ago, patient fell backwards on bath tub, since then he has been bleeding from the rectum continuously. The hemorrhage was more profuse the first day. Nose began to bleed on day of admission at 4:30 p. m. and there has been a steady trickle since that time. Bowels act once daily, there is pain in the region of the rectum on emptying the bowel. He also complains of pain in the region of the umbilicus. There is a burning on voiding urine which is of a dark muddy color. The patient is extremely drowsy, he nods between questions and goes to sleep immediately after being aroused.

Physical Examination.—Male, negro, 25 years of age, well-nourished. Temperature 98° F. (36.66° C.); pulse 108; blood pressure 178–130 mm. **Hg. Head:** Round, flat face, thick lips, flat nose, edema of eyelids, pupils react to light and accommodation; mucous membranes very pale; tongue broad, thin, covered with a grayish coat, ulcer on lower lip. **Heart:** Apex in the fifth interspace 4 in. (10.16 cm.) from midsternal line, a soft blowing systolic murmur at apex transmitted to the axilla; arteries are soft, pulse rapid and of high tension. **Lungs:** Negative. **Abdominal Organs:** Without findings except umbilical hernia; the skin is cool, dry and scaly. **Bones and Joints:** Negative. **Muscles:** Well-developed and

hard. Epitrochlears, cervical and inguinal lymph-nodes are palpable. Reflexes, normal. Blood exudes from the nose and rectum.

Urine.—Clear, pale, straw-colored; specific gravity, 1012; alkaline; albumin +; casts + + (finely granular).

Blood.—Red cells, 2,400,000; leukocytes 8,200; polymorphonuclears 87 per cent.; small lymphocytes 9 per cent.; large mononuclears.

Functional Tests.—Blood urea, 232.2 mg. per 100 c.c.

Eye-grounds.—The nerve heads are pale and there are areas of retinal exudate. Hemorrhage in both eyes near the disk. The macular regions do not show any change.

Course.—One hour after admission, December 9, 1920, patient bleeding from rectum and nose; 10 c.c. of normal serum given; blood-pressure 178–130. Temperature subnormal; rectal examination reveals no cause for hemorrhage. There is no history of hemophilia in the patient's family; 10 c.c. horse serum at 6:00 P. M. December 10, patient has not bled any to-day, is drowsy, sleeping all the time. December 11, 1920, patient had a convulsion last night lasting one minute and another one this morning. The urine is incontinent, he is comatose and the breathing stertorous. December 12, 1920, patient did not come out of coma and died at 12:20 P. M.

Clinical Diagnosis.—Chronic diffuse glomerulonephritis (end stage), secondary anemia, albuminuric retinitis, and uremia.

ILLUSTRATIVE CASE NO. IV.—Horace Martin, male, colored, age 26. Admitted to Memphis General Hospital, October 15, 1921. Died October 21, 1921.

Chief Complaints.—Shortness of breath, and tight drawing sensation in abdomen.

Family History.—Negative.

Past History.—A previous similar attack in July, 1920; otherwise negative.

Present Illness.—The present illness began ten days ago. Onset was gradual. He first had an uncomfortable drawing sensation of stiffness in the legs about ankles and knees. The swelling would disappear after a night's rest. Three days after onset he began to have shortness of breath. He was forced to quit work. There was puffiness about the eyes and abdominal swelling followed. The above symptoms have rapidly grown worse. He has nycturia, 4 to 5 times. He is constipated and has anorexia. No other symptoms.

Physical Examination.—Well-developed, well-nourished negro, male, age 26. Lies quietly in bed; has a very anxious expression on his face and is gasping for breath. Temperature 97° F. (36.11° C.), pulse 70, respiration 18, blood-pressure 190–120. *Head:* Normal contour; hair appears lifeless, is falling out, though not in circumscribed areas. *Face:* Swollen and there is puffiness about the eyes. *Teeth:* Very faulty. *Tongue:* Large and pale; right border is notched. *Tonsils:* Small and ragged. *Pharynx:* Hyperemic. *Neck:* The vessels are very promi-

ment. Cervical and submental adenopathy. *Chest*: Symmetrical in development and respiratory excursions are rapid and not full. *Lungs*: Tactile and vocal fremitus diminished over both bases posteriorly. Moist râles are heard over this area. Breath sounds are harsh at apices. *Heart*: Apex in seventh interspace $1\frac{1}{2}$ ins. (3.81 cm.) inside the mid-clavicular line. Right border at right border of sterum; left border in midclavicular line. Sounds are very rough, no murmurs. Aortic second accentuated. *Abdomen*: Distended; dulness below stomach. No distinct fluid wave. *Liver*: Palpable 1 in. (2.54 cm.) below costal arch. *Spleen*: Not palpable. The epitrochlear glands are enlarged. The extremities are edematous. The reflexes are normal. The sexual organs are negative.

Urine.—October 16, 1921, color pale; specific gravity, 1010; reaction acid, albumin negative; glucose, negative; casts negative; leukocytes and pus cells a few.

Blood.—Red cells 4,000,000; leukocytes 8,800; polymorphonuclears 75 per cent.; small lymphocytes 21 per cent.; large mononuclears 4 per cent.; Wassermann + + + +. No parasites.

Course.—October 17, 1921, patient dyspneic, generalized edema, tongue anemic, a patchy looking area on right margin. *Heart*: Apex rather diffuse, is displaced inward, is located in the sixth interspace. Cardiac dulness extends to the right of the sterum. Left border of the heart inside the left nipple line. Sounds are valvular in quality with marked roughening; no murmurs; aortic second distinctly accentuated. *Lungs*: Tactile fremitus diminished over both bases posteriorly. Voice and whispered sounds diminished over bases with moist râles. No tracheal tug. *Abdomen*: Tympany above, flatness in flanks. *Liver*: Tender. Dulness from fifth rib to two fingers' breadth below costal arch. *Spleen*: Not palpable. October 18, 1921, no marked change in patient's general appearance, though the impaired pulmonary resonance over bases posteriorly is more marked and the heart sounds are very rough. There is an area of bronchovesicular breathing over the right lower lobe posteriorly. October 19, 1921, an indistinct to-and-fro friction rub heard between the second and fifth ribs to the left of the sternum above crossing to right below, marked orthopnea. October 20, 1921, patient unimproved. Orthopnea, suffering great pain in the chest. A very loud to-and-fro friction rub heard over entire precordium. Heart sounds are distant. Lungs show areas of diminished resonance posteriorly, right middle and lower, an area of tubular breathing over middle of right lobe posteriorly. Abdomen tympany above, flatness in flanks. October 21, 1921, patient gasping for breath, pulse almost imperceptible. Dulness over bases, lower middle right almost completely flat. Patient rapidly on decline. Patient unconscious, cannot be aroused. Died at 10:40 A. M.

Urine.—October 18, 1921, pale, specific gravity 1010, acid, albumin negative, many hyalin (small, large and coarsely granular) casts.

Functional Tests.—October 20, 1921, phthalein 15 per cent. in 2 hours. Blood urea 70 mg. per 100 c.c. Creatin 2.35 mg. per 100 c.c.

Clinical Diagnosis.—Chronic diffuse glomerulonephritis (end stage), myocardial insufficiency, pericarditis, uremia, and bronchopneumonia.

AUTOPSY REPORT.—Horace Martin, October 24, 1921.

External Examination.—Body that of a large well-developed, muscular, well-nourished colored male, 179 cm. (5 ft., 10½ ins.) in length. Edema of the face and neck.

Internal Examination.—Small amount of clear straw-colored fluid in the pelvic cavity. Congestion of the capillaries of the small intestines. Clear yellow fluid in both plural cavities. A large amount of slightly cloudy yellow fluid with masses of fibrin in pericardial sac with slight congestion of the serous surfaces. Thymus negative. **Heart:** Greatly enlarged, 580 grams (1.28 lbs.). Walls thickened, left ventricular wall 2 cm. Myocardium reddish brown, firm. All chambers dilated; valves, coronary arteries, pulmonary arteries negative. Aorta and thymus, negative. **Lungs:** Very large, edematous, heavy, less air than normal. On section large amount of rust-colored fluid. **Spleen:** Enlarged 430 grams (.95 lbs.), firm. On section, deep red and level with cut edge. **Liver:** Enlarged, lobulated, externally and on section prominent, center deep red. Gall-bladder and ducts negative. **Kidney:** Small, 110 and 90 grams (.24 and .2 lb.). Capsule adherent, surface finely nodular, gray, firm, cut with resistance, cortex narrow, .4 cm., striations indistinct, blood-vessels not prominent. Pelves and ureters negative. **Stomach and Intestines:** Throughout entire extent, mucous membrane swollen, covered with large amount of gray, granular material. **Bladder:** In mucous membrane are scattered bluish-white translucent nodules 1 mm. in diameter with black periphery, singly or in groups of as many as five in number; their individuality is retained, being freely movable with mucous membrane, most numerous in trigone. Pancreas, mesenteric lymph-nodes, seminal vesicles, testicles, negative.

Bacteriology.—Heart's blood and pericardial sack, negative.

Microscopical Kidney.—Many glomeruli are enlarged, filling the whole capsule in which there is marked intracapillary proliferation. Others show partially destroyed glomeruli in which a part of the loops has undergone hyalinization, while other glomeruli are completely changed to hyalin clumps. There is very little or no proliferation of the capsular epithelium. In places there is quite marked pericapsular thickening. **Tubules:** In many areas there is distinct island formation of the tubules, i.e., dilated tubules lined by a low type of epithelium, surrounded by increased connective tissue. In some areas the tubular epithelium shows some granular and fatty degeneration though this is not marked. Many tubules contain casts. Interstitial tissue is distinctly increased. There are rather large areas of small cell infiltration and old connective tissue is quite in evidence. **Blood-vessels:** There is distinct thickening of the walls of the blood-vessels in the boundary zone. The smaller vessels show distinct arteriosclerotic changes.

Microscopic Diagnosis.—Chronic diffuse glomerulonephritis (end stage), secondary contracted kidney.

Anatomic Diagnosis.—Chronic diffuse glomerulonephritis (secondary contracted kidney), hypertrophy and dilation of heart, general chronic passive congestion, serofibrinous pericarditis (sterile), and bronchopneumonia.

THE FOCAL NEPHRITIDES

Acute Focal Glomerulonephritis.—This usually begins suddenly and simultaneously with the causative infection. As a rule the patient complains of no general symptoms. There may be some difficulty on voiding or pain in the lumbar region. The symptom which usually calls the patient's attention to a disturbance in the kidney is the bloody appearance of the urine. On physical examination, no edema is found, the blood-pressure is not increased, and there is no evidence of cardiac hypertrophy. The urine usually shows a bloody appearance, much albumin due to the blood present, casts and many red blood-cells and leukocytes. Bacteria are often present.

The functional kidney tests are usually good. The quantity is normal, unless reduced as results of fever of the causative infection. The salt, water, and nitrogen excretion is good, and there is usually no retention of urea in the blood. It is quite possible that the focal lesions may be so extensive as to produce marked insufficiency with uremia, as the author has seen in one case.

Uremia in none of its forms, however, occurs as a rule. The absence of eclamptic uremia is explained by the absence of hypertension and dropsy, eclamptic equivalents by the absence of arteriosclerosis in various areas and true uremia by the absence of nitrogenous retention in the blood.

The diagnostic feature of acute focal glomerulonephritis is the presence of hematuria with the absence of increased blood-pressure and cardiac hypertrophy. It may sometimes be difficult to decide between a subsiding acute diffuse glomerulonephritis and acute focal glomerulonephritis, as the following case shows:

Mr. L. S., white, age 34, married, merchant, seen October 30, 1921. Chief complaint, shortness of breath, swelling of feet and ankles, and pain in lumbar region (bilateral). Family history, negative. Past history, pleurisy, chills and fever. Appendectomy 1907. *Present Illness:* About two months ago was hit by a stone, fracturing nasal bone. This was infected and he was operated on. Last week he was taken with severe pain in lumbar region and swelling of face. Later he noticed shortness of breath, breathing being especially difficult at night. Swelling of ankles, knees and chest. Some frontal headache. No difficulty with urination. *Physical Examination:* Temperature 96° F. (36.66° C.); pulse 72; blood-pressure 142-82. Patient is undernourished, rather pale in appearance, slight swelling of the right side of the face. Many crowns and bridges. Throat, red. *Chest:* Possibly slight impairment of motion at right apex. Slight increase of vocal fremitus at both apices.

Pulsation in the vessels of the neck. Bronchovesicular breathing in right suprascapular area, increased whispered voice sounds. A few inconstant râles at left apex. *Heart*: Apex beat in normal position, an occasional extra systole; otherwise negative except for possible slight accentuation of aortic second sound. *Abdomen*: No tenderness; negative. *Knee-jerks*: Active. No edema of extremities. *Blood*: Leukocytes 8000; polymorphonuclears 73 per cent.; small lymphocytes 23 per cent.; large mononuclears 3 per cent.; basophils 1 per cent.; blood urea 64.5 mg. per 100 c.c.; Wassermann negative. *Urine*: Cloudy; amber; specific gravity, 1026; acid; albumin + + +; sugar negative; microhyalin, granular and blood casts; pus cells + + +; red blood-cells.

With rest in bed, on diet restricted to 50 grams of protein, for three weeks the patient felt well, the slight swelling of the face subsided, the blood-pressure returned to 120-70, the blood disappeared from the urine. After being up for two weeks, the urine showed blood macroscopically, specific gravity, 1018, albumin + + + +; no casts; blood-pressure 118-65, and blood urea 45 mg. per 100 c.c. This is an illustration of Volhard's statement that an original acute diffuse glomerulonephritis may recur as the nonhypertonic, focal type. The combination of edema and hematuria without hypertension, generally, is in favor of a subsiding, diffuse glomerulonephritis associated with nephrosis.

The treatment of acute focal nephritis is much the same as that described for acute diffuse glomerulonephritis—**rest in bed**, and **slightly restricted protein diet**. As in acute diffuse nephritis the general condition may grow worse under confinement to bed, when the patient may be allowed to be up and take moderate exercise, provided the hematuria is not increased thereby. Styptics, such as calcium salts, gelatin, ergot, adrenalin, coagulose and lead salts are without any beneficial effect. Sometimes the hemorrhage may be so great and associated with pains in the lumbar region as to suggest the advisability of surgical intervention. In such cases **decapsulation** under local anesthetic with as little handling and trauma of the kidney as possible will be attended with good results. Of course any focal infection present should be removed if possible. The immediate result of such operations is, however, an increase of the hematuria which subsides after a short time.

The prognosis of acute glomerulonephritis is good, except in cases associated with severe sepsis. There is a great tendency for these cases to recur and they sometimes pass over into chronic focal glomerulonephritis.

PATHOLOGY.—The kidney in acute focal glomerulonephritis offers no characteristic appearance macroscopically. As the name indicates, while the changes are of the same character as in the diffuse form, the lesions occur only focally and not diffusely. They are usually met with as an accessory finding associated with some other condition causing death. Fahr has pointed out that anatomically it might be difficult to differentiate a focal glomerulonephritis from a beginning or healing acute diffuse glomerulonephritis. The same author has called attention

to the absence of red cells in the glomerular loops as an indication of a still active nephritis, while the presence of blood here might indicate a subsiding nephritis.

Chronic Focal Glomerulonephritis.—These cases in their onset and course resemble very closely the chronic diffuse glomerulonephritis without kidney insufficiency; many cases are latent, others present pain in the lumbar region, and others may be associated with nephrosis, presenting more or less severe edema. The hematuria without increased blood-pressure and without heart hypertrophy is again the differentiating characteristic. The kidney function is usually unimpaired.

Septic-Interstitial Nephritis.—This occurs almost exclusively as a result of acute streptococcal sepsis, as after scarlet fever, diphtheria, necrotizing angina and wound infections. The indications from the symptoms, physical findings, laboratory and special examinations are usually lacking.

PATHOLOGY.—Macroscopically these kidneys do not present a characteristic appearance. If the microscopical changes are slight, the kidney does not vary from the normal appearance macroscopically. If, however, the interstitial infiltration is marked, the kidney may be swollen, moist, as the result of serous infiltration, and soft in consistency. The cortex and pyramidal substance are well differentiated and the markings of the cortex are indistinct. The macroscopical appearance may indeed be so characteristic as to render a diagnosis possible,—brownish hemorrhagic streaks in the cortex corresponding to brownish flecking on the outer surface, enlargement of the kidney, differentiation of cortex and pyramids (Aschoff).

Microscopically, in mild cases there are small foci of round cell infiltration distributed in the interstitium of the cortex. These foci consists chiefly of lymphocytes and plasma-cells; these areas of infiltration may be between the tubules, separating them and by pressure may destroy them. The glomeruli withstand the destructive process much longer than the tubules, though coagulated masses may be present in the intracapsular space. The capillary loops in the beginning of the process are well filled with blood, but later the blood there is considerably diminished.

Hemorrhage may be present in the larger areas which are found by preference in the boundary zone. When the areas of infiltration reach considerable size they may be seen as boat-shaped areas with base directed towards the outer surface. Other areas of the parenchyma may be intact. The vessels and heart are not changed from the normal. It is questionable whether these kidneys develop into the primary contracted kidney; Aschoff thinks that they may rarely do so.

Embolic Focal Nephritis.—This form of nephritis is usually associated with infectious endocarditis due to the *Streptococcus viridans*. The symptoms and findings referable to the kidneys are obscured by those due to the infective endocarditis. They may, however, resemble those found in focal glomerulonephritis. These cases are, however, more

likely to be complicated by the picture of nephrosis on the one hand and by insufficiency on the other as shown in an inability to concentrate with hyposthenuria.

PATHOLOGY.—Macroscopical.—The kidney is not enlarged, is of firm consistency and very rich in blood. The outer surface and cortex are brownish, and the pyramids dark brown. The cortex and medulla are well differentiated and the cortical markings are distinct. Hemorrhages are not recognizable macroscopically.

Microscopical.—Many of the glomeruli contain emboli of bacteria, usually the *Streptococcus viridans*, but other organisms have been found. These emboli produce necrosis of a part or the whole of the glomerulus. In the early stages the bacteria, as well as degenerated cells, fibrin and red blood-cells may be demonstrated. The inflammatory reaction around the necrotic areas is usually slight. If the emboli are situated in the peripheral-lying loops, there may be seen a pericapsular leukocytic infiltration. Bowman's capsules are generally empty, but coagulated masses and red blood-cells may be present. If the vasa efferentia are blocked by emboli, the reaction may be so great as to produce miliary abscesses.

The proximal convoluted tubules may show granular degeneration. The tubules may be destroyed; in older cases the necrosis of the glomeruli is replaced by scar tissue. The interstitial tissue is also increased in this stage and as a result of the destroyed glomeruli, the tubules belonging to them show granular degeneration.

THE SCLEROSES

Introduction.—Chronic hypertensive states have been the subject of much confusion with respect to etiology, clinical manifestations and the underlying pathology. For a long time they were all grouped under the term chronic interstitial nephritis, represented by the primary contracted kidney. About 1876 Mahommed introduced the term "the pre-albuminuric stage of Bright's disease" by which he would indicate, that there was a period, longer or shorter, of augmented blood-pressure, a period during which the encroachment of the disease could be foretold and perhaps forestalled. At about this time Von Basch began to write of "Latent Arteriosclerosis" and Huchard of "Presclerosis," both indicating that rising pressures often preceded anatomical changes in the kidneys but were due to arteriosclerosis latent or manifest in some part of the body, and did not necessarily represent the incipient stage of renal disease in the ordinary sense.

Also about this time Sir Clifford Allbutt began to elucidate his ideas on this condition and developed a clinical concept to which he gave the name hyperpiesis, believing that the hypertension was due to functional hypertonus of the arterioles, but that arteriosclerosis might develop later as the result of the hypertension. Janeway designated a similar condition as hypertensive cardiovascular disease. By this time the pathologists (Jores, Gaskell, Fahr and others) had shown that the kid-

ney, represented by the term chronic interstitial kidney, primary contracted kidney, did not develop from an inflammatory process at all, but was the result of arteriosclerotic processes affecting the small and smallest blood-vessels of the kidney. In 1914 Volhard and Fahr published their observations made together in a monograph "Die Brightsche Nieren Krankheit." They designated benign hypertension as a clinical condition in which there could be found no evidence of impaired kidney function and represented by kidneys showing pure arteriosclerosis of the small and smallest blood-vessels; macroscopically the kidney may be contracted or noncontracted, while the malignant or combination form was a condition showing impaired kidney function and represented by kidneys which showed in addition to marked arteriosclerotic changes, also changes of an inflammatory or degenerative kind.

Recently Barker has divided the chronic hypertensive states into four groups clinically: (1) Incipient arterial hypertension often accidentally discovered; (2) relatively early chronic arterial hypertension without obvious signs of renal or arterial disease (so-called hyperpiesia, essential hypertension, idopathic hypertension, etc.); (3) the more advanced stage of chronic arterial hypertension, but before the appearance of serious complications; and (4) late stages of chronic arterial hypertension, with serious complications (cerebral, cardiac, renal, etc.).

This author would seem to regard these groups as different stages of the same process. "If patients in whom the diagnosis of so-called primary, or essential hypertension has been made and in whom the disease process has not been arrested at a relatively early stage by treatment, be followed long enough, they will, I venture to say, be found sooner or later to suffer from the same kinds of accidents, and will ultimately make their lethal exitus by the same routes (cerebral apoplexy, myocardial insufficiency, uremic poisoning, or terminal infection) as are characteristic of the histories of patients in whom a diagnosis of arteriosclerotic hypertension, or of nephropathic hypertension, has been made."

The author believes that at the present it is better to distinguish with Volhard and Fahr two groups of scleroses: (1) Benign hypertension, and (2) malignant hypertension (the combination form).

BENIGN HYPERTENSION

(Essential Hypertension, Hyperpiesis, Hypertensive Cardiovascular Disease, Red Granular Kidney, Genuine Contracted Kidney, The Large Smooth Kidney with Diffuse Presclerosis or Arteriosclerosis of the Kidney Vessels)

Etiology.—The etiology of benign hypertension is as obscure as that of arteriosclerosis in general; but all those factors which favor the occurrence of the latter also favor the development of nephrosclerosis.

AGE AND SEX.—In 268 cases of benign hypertension, Volhard and Fahr found that the greatest number occur in the fifth and sixth decades; and that men are possibly more frequently affected than women.

The following table including Volhard and Fahr's cases and 100 of the author's will show the age and sex distribution:

Volhard and Fahr's Cases				Author's Cases			
Age	Period	Male	Female	Total	Male	Female	Total
To	-20	1 (.4%)	1 (.4%)
21	-30	2 (.8%)	2 (.8%)	3%	3%
31	-40	8 (3.2%)	7 (3%)	15 (6.2%)	3%	3%	6%
41	-50	31 (11.5%)	15 (6.5)	46 (18)	11%	19%	30%
51	-60	48 (14)	34 (16)	82 (30)	25%	13%	38%
61	-70	42 (15.5)	40 (14.5)	82 (30)	12%	5%	17%
71	-80	18 (7%)	19 (7%)	37 (14)	3%	1%	4%
81	-90	2 (.8%)	2 (.8)	1%	1%	2%
91	-100	1 (.4)	1 (.4)
		149	119 (48%)	268	58%	42%	100

In 50 cases Meara found the age distribution as follows: 56 per cent. fell between 45 and 55 years, and 68 per cent. fell between 45 and 60 years.

HEREDITY.—Attention has often been called to the influence of heredity on the vascular system. It has often been noted that different members of the same family show a tendency to hypertension. The stocky build, short, thick neck, red face and tendency to obesity—the *habitus apoplectic*—is recognized as a family trait. Migraine, a notoriously hereditary affection, is frequently associated with hypertension.

Familial thyreopathies also predispose to hypertension. Osler used to emphasize the fact that one may start life with different kinds of tubing. Barker has recently added that "this tubing, the vasomotor nervous system innervating it, and the organs of chemical regulation in the body that yield chemical substances that impinge upon both, depend largely upon the source from which the person springs—that is, upon family stock." In 100 cases of benign hypertension there appears in the family history a record of Bright's disease 4 times, of arteriosclerosis 1 time, of paralysis 12 times, of apoplexy 5 times, of heart disease 12 times, of kidney trouble 1 time, and of diabetes 1 time.

WEAR AND TEAR.—Benign hypertension is frequently found in persons who hurry and worry. Its subjects are often found in the upper classes of society, who occupy responsible positions with their necessary mental strain. Physical strain is also an important factor, but not so much so as the former as shown by the fact that only 15 of the 100 cases occurred in a general city hospital as compared with 85 cases in private consultation practice over the same period of time. The series is represented by a great variety of occupations, laborers, housewives, school-teachers, planters, merchants, insurance men, ministers, college presidents, lawyers, physicians, bankers, real estate men, cotton brokers, sheriffs, horse trainers, clerks, contractors, theater managers, etc. The

wear and tear attendant upon any of these callings and the effects of the same are possibly due to the make-up of the individual.

INFECTIONS.—Infections of various kinds also appear in the record of the past history of this series. But it is difficult to estimate with any degree of accuracy the influence of these upon benign hypertension. They as other series show the relative infrequency of syphilis in the record. While Wassermann's were made on each case of the series, it was positive in only five of the one hundred cases.

INTOXICATIONS.—Various intoxications either of an exogenous or endogenous nature have been accredited as causes of atherosclerosis of the kidney vessels. Among the former are alcohol, tobacco, coffee, tea, lead, mercury and zinc; among the latter are the various poisons arising in the gastro-intestinal tract.

The influence of alcohol and tobacco, as well as tea and coffee, is difficult to estimate. It is pointed out by Volhard and Fahr that the Munich-beer heart and the so-called idiopathic cardiac hypertrophy might depend upon hypertonic kidney sclerosis, although the autopsy report on the kidneys in these cases is normal—the kidney sclerosis being overlooked, if careful microscopic examination, including special methods of staining are not carried out.

The general opinion is, however, that alcohol is not a marked factor in the production of kidney sclerosis. The views with respect to tobacco are more at variance. The great frequency with which nephrosclerosis occurs in women would discount tobacco as an important factor. The excessive use of tea and coffee may be favorable for its production. The evidence for any of these including the heavy metals, and gastro-intestinal intoxications is not specially noticeable in the author's series.

METABOLIC DISEASES.—Gout, diabetes, obesity, and the tendency to stone formations have been discussed in their relationship to arteriosclerosis of the kidney. In the author's series there were many overweight and 5 in whom marked obesity existed, and also 6 in whom either frank diabetes or a markedly lessened sugar tolerance existed.

Symptomatology.—The onset of benign hypertension may be quite gradual, indeed a high blood-pressure may exist for several years without producing any symptoms, and be discovered accidentally as in the routine examination for life insurance or other cause. Occasionally a cerebral apoplexy may be its first manifestation, or there may be mild symptoms on the part of the arterial system, *e.g.*, nosebleed, flushes of heat, and throbbing in the ears.

However, the symptoms of which the patients usually complain first are those referable to the heart; *i.e.*, hypertension usually makes itself manifest by symptoms when the left heart begins to fail to empty itself against the increased peripheral resistance. Indeed, the cardiac symptoms stand in the foreground throughout the clinical course of the disease.

At first these are the symptoms of relative myocardial insufficiency, which, together with their pathologic physiology, has been discussed under the circulatory nephropathies. There is shortness of breath on

exercise, sometimes associated with palpitation. There may be a sense of pressure beneath the sternum, or a sense of constriction in the chest after a heavy meal or excess in *Baccho*. Disturbances of sleep are quite common. The patient cannot lie on his left side on account of the throbbing of the pulses in his ears, which keeps him from going to sleep. The sleep may be restless, disturbed by dreams and nightmares. Frequently the patient awakens suddenly with a start. Attacks of difficult breathing, closely simulating bronchial asthma, are likely to occur especially at night. There may be swelling of the ankles and lower limbs, occurring during the day to disappear after a night's rest.

These attacks of relatively myocardial insufficiency have quite distinct characteristics in benign hypertension. They are borne over a long period of time, and sometimes disappear without any special treatment, and the objective manifestations of myocardial insufficiency may be absent also for a long time.

There is frequently a history of a repetition of these attacks after disappearance, before finally the manifestations of complete cardiac decompensation set in; at this time there is dyspnea even while the patient is at rest, stasis bronchitis takes the place of the paroxysmal attacks of dyspnea, and there is cough with expectoration, arrhythmias, digestive disturbances and symptoms of stasis in other organs.

RENAL SYMPTOMS.—These are not prominent in benign hypertension. The patient may complain of nycturia and there may be a slight night polyuria. This is, however, not to be confused with the nycturic polyuria of kidney insufficiency; that of cardiac origin is usually associated with a day oliguria in contradistinction to that of nephritic origin which is usually associated with a day polyuria.

Increased thirst as in chronic diffuse glomerulonephritis in the end stage is not present in benign hypertension with well-compensated heart, but may be present with decompensation. The symptoms with reference to the arterial system are quite numerous and varied. These have been discussed in connection with eclamptic equivalents in the section on Uremia.

As stated above, not infrequently apoplexies occur, as well as mental disturbances such as progressive dementia and insanity and transitory paralysis as the result of focal cerebral softening from thrombotic processes. More frequent, however, and more prominent are those symptoms due to functional disturbance produced by arteriosclerosis of the cerebral vessels. Headaches, frequently of the type of migraine, dizziness and fainting spells occur. Transitory aphasia, amaurosis, deafness, paralyzes, maniacal conditions and epileptiform attacks may also be present. Cheyne-Stokes' breathing is possibly also an arterial symptom often met with. Severe attacks of distressed tachypnea without the presence of physical signs in the chest, which Pal has designated cerebral high tension tachypnea, sometimes occur. The relief afforded these by lumbar puncture would indicate that they are caused by increased intracerebral pressure. Hemorrhages from various sources, nosebleed often difficult to stop, and hematuria are also met with among

the arterial symptoms. Recently one of the author's patients had hemoptyses, for which no other cause than the hypertension, which was quite marked, could be discovered.

Hemorrhages may also occur in the subcutaneous tissues as the result of slight traumata. Attacks of angina pectoris and angiospastic symptoms in other areas as angina abdominalis, intermittent claudication and "dead fingers and toes" are not infrequently met with.

PHYSICAL FINDINGS.—General Appearance.—These patients often appear as if in robust health, the complexion is ruddy, the habitus is plethoric, they are active and frequently are overweight, with a tendency to obesity, though thin people may also be the subject of benign hypertension.

The Blood-pressure.—Increased blood-pressure is one of the pathognomonic signs of benign hypertension. There is some difference of opinion as to just what constitutes an increased pressure. The normal pressure varies according to age. The general average for the different ages may be stated as follows:

15-30.....	123
30-40.....	126
40-50.....	128
50-60.....	133
60-70.....	138

These figures as the result of various physiological conditions, such as time of day, sleep, posture, eating, exercise, emotional states, menstruation may vary 19 or 20 points up or down. The diastolic pressure is normally below the 100 mm. Hg., usually in grown persons from 70 to 80. It is much more constant under various physiological conditions than the systolic pressure—rarely varying more than 6 or 8 points.

In 268 cases of benign hypertension, Volhard and Fahr found values above 200 in 40 per cent., between 170 and 200 in 40 per cent., and below 170 in 20 per cent. In the author's cases, there were values above 200 in 13 per cent., between 170 and 200 in 48 per cent., and from 150 to 170 in 39 per cent.

In the greater number of cases the hypertension is maintained at a more or less constant level, but under certain conditions the systolic pressure may vary up or down—down in early cases as the result of treatment. Often also with the onset of cardiac decompensation the systolic pressure may fall and the diastolic rise. More rarely is there a variation upward, which Pal designates as crises and these rises are usually associated with alarming symptoms of a cardiac or cerebral nature.

The Heart.—As a result of hypertension the heart is regularly enlarged. The hypertrophy at first involves the left ventricle, which it may be difficult to demonstrate at the time by physical signs. By the time relative myocardial insufficiency has been established, the apex beat will be displaced downward and outward and show a heaving

character. The area of cardiac dulness will be increased to the left, and often early, but more often later in the disease, the supracardiac area of dulness will be widened as the result of dilatation of the aorta. The aortic second sound is markedly accentuated, as is also the first sound at the apex. There is frequently a presystolic gallop rhythm. In this stage the pulse is usually regular, but may be a little quickened. The hypertrophy will now often be better shown by x-ray examination, which reveals the so-called sock heart, which is due to the hypertrophied left ventricle. The electrocardiogram will show left ventricular preponderance. With the onset of complete cardiac decompensation right ventricular hypertrophy and dilatation will be added to the left ventricular hypertrophy and the area of cardiac dulness will be increased to the right and to the left. The enlargement often is such as to deserve the name *cor bovinum*.

The presystolic gallop rhythm may be replaced by a protodiastolic rhythm. There may be seen sometimes a postsystolic retraction of the chest wall in the apex region and a diastolic shock felt. Possibly as a result of the brusque filling of the flaccid, incompletely emptied ventricle from the increased pressure in the left auricle, an indistinct third heart sound may be heard. Not infrequently the systolic mitral murmur of relative myocardial insufficiency may be heard. The orthodiagram shows all of the diameters of the heart enlarged.

On an average the median right equals 4.6 cm.; the median left 11.3; and the longitudinal 17.5. Arrhythmias are now quite frequently present, the most common irregularity being premature contractions. Pulsus alterans is discovered in taking the blood-pressure much oftener than it was formerly supposed to occur. The various stages of heart-block may be observed, and complete disassociation of the auricular and ventricular rhythm is sometimes seen. Auricular fibrillation is not usually seen until the late stages of myocardial insufficiency or unless the benign hypertension is associated with mitral stenosis.

Valvular diseases are not infrequently associated with benign hypertension. The one most often met with is aortic regurgitation, which may arise on an arteriosclerotic or leutic basis. Occasionally also aortic stenosis or mitral stenosis may occur on an arteriosclerotic basis.

An abnormal presystolic pulsation and swelling of the veins of the neck may be made out. The liver is enlarged and may be felt to pulsate. The venous pressure is markedly increased. Under certain conditions such as very advanced age, emaciation, weakening disease and prolonged enforced rest, and disturbances in the blood supply to the heart muscle by sclerosis of the coronary arteries, cardiac hypertrophy may be absent, or slight.

Edema.—This is lacking in the compensated stages of hypertension. In the stage of decompensation it is frequent and may reach extreme grades.

LABORATORY EXAMINATIONS.—Urine.—This may be entirely normal as to color, quantity, specific gravity, albumin and casts for a long time.

Frequently, however, a trace of albumin and a few casts may be present. With the onset of myocardial insufficiency it may show the characteristics of the stasis kidney,—oliguria, high fixed specific gravity, albumin, casts, leukocytes and red blood-cells. With the elimination of edema there may be polyuria with low specific gravity (see *Circulatory Nephropathies*).

Blood.—There is usually no evidence of anemia; on the contrary, there is more frequently a moderate polycythemia which is in marked contrast to the blood findings in the end stage of diffuse glomerulonephritis and the combination form.

SPECIAL EXAMINATIONS.—*Ophthalmoscopic.*—Eye-ground examinations are of great diagnostic value. It is sometimes the only evidence as to whether a given case is to be regarded as benign or malignant hypertension. In the greater number of cases of benign hypertension the eye-grounds are normal; frequently, however, the retinal arteries will appear contracted and tortuous with thickened walls. The veins will be widened. Due to arteriosclerosis, small hemorrhages and areas of degeneration may be present, but the characteristic changes of albuminuric retinitis do not occur.

Kidney Functional Tests.—The second pathognomonic finding in benign hypertension is the absence, as a rule, of impaired functional capacity of the kidney, as determined by the usual functional tests.

According to Volhard, there are three groups of cases with respect to the water test. In the first group which contains the greatest number of cases, 1500 c.c. of water taken on a fasting stomach is excreted in four hours and the greater part in the first two hours with lowering of the specific gravity, *i.e.*, as in health.

In the second group, which includes quite a number of cases, the test is excessive, *i.e.*, more than 1500 c.c. are excreted in four hours. This is likely to occur in cases which show transitory hypertension, *i.e.*, in cases which under treatment show a tendency to a falling of the blood-pressure. The third group shows a poor result, *i.e.*, less than 1500 c.c. are excreted in four hours or the total quantity is excreted over a much prolonged time. This is especially likely to occur in cases with marked cardiac decompensation and in cases which have been on a dry diet for a long time because a greater part of the water taken in is retained by the thirsty tissues.

Concentration Test.—On an absolutely dry diet, the specific gravity of urine rises regularly as in health. It may reach 1025 or 1030 after 8 to 12 hours. This test is difficult to carry out in cases associated with cardiac decompensation. In the latter cases the ability of the kidney to excrete water, salt and nitrogen is the same as in the stasis kidney (*q.v.*).

Phenolsulphonaphthalein Test.—In compensated cases the phthalein output is normal, *i.e.*, 50 per cent. or more in two hours and 10 minutes. In cases with myocardial insufficiency the output may be low and return to normal upon the restoration of compensation.

Meara reports the following findings with respect to this test:

<i>Cases Observed</i>	<i>Phthalein Output in 2 hrs.</i>
5	70-80%
11	60-70%
8	50-60%
6	30-40%
1	5%

Retention Tests.—Meara found the following values as to uric acid, urea nitrogen, non-protein nitrogen and creatinin in hyperpiesia:

Uric acid in the blood (43 cases); 44 per cent. showed some retention and 56 per cent. normal values.

Urea Nitrogen (42 cases); taking 20 mg. or less per 100 c.c. as normal, 20 to 25 mg. per 100 c.c. as debatable, 77.6 per cent. showed normal values and 21.6 per cent. frank retention, but in only 4 did the values run above 30 mg. and the highest of these was 48 mg.

Non-protein Nitrogen (12 cases); there were 35 mg. per 100 c.c. or less in 3 cases; from 35 to 45 mg. in 6 cases; 45 to 50 mg. in 2 cases; and 78 mg. in 1 case.

Creatinin (16 cases); 11 cases showed 3 mg. per 100 c.c. or less; 4 cases 3 to 4 mg.; 1 case 4 to 8 mg. (3 mg. or less is taken as normal).

Volhard and Fahr made non-protein nitrogen estimations in the blood fifty-eight times in benign hypertension and found values varying within normal limits, i.e., up to 50 mg. per 100 c.c. They state that in cases of severe cardiac insufficiency, shortly before death and in cases in which edema is being eliminated somewhat higher values were found.

In the author's cases the modified Mosenthal test has been normal or shown the characteristics of the stasis kidney. The phthalein test was within normal limits in compensated cases, but may be markedly lowered in severe myocardial insufficiency. *The blood urea* has been within normal limits. In compensated cases there have been from 19.5 mg. to 50 mg. per 100 c.c. of blood.

The average of 55 cases was 34.7 mg. per 100 c.c. In severe decompensation and during the elimination of edema the upper limits of normal (50 mg. per 100 c.c.) has been usual, one time rising to 62 mg. per 100 c.c.

Basal Metabolism.—According to Mosenthal and Marks, the basal metabolic rate in cardiorenal disease without dyspnea is normal + 10; in cases with dyspnea it is from + 25 to + 50. Barker states that some of the hypertensions have an increased rate, some a decreased rate and many a normal rate.

Diagnostic Features.—(1) It usually occurs after the fiftieth year of life and is of quite frequent occurrence.

(2) It begins and runs its course as a cardiovascular disease. If a cerebral vascular accident is not the first manifestation, the first symptoms begin to make themselves noticeable when the left ventricle begins to weaken as it is no longer able to empty itself against the increased resistance. The symptoms are those of relative myocardial insufficiency, and the patient oscillates a long time between compensation and complete decompensation. Finally the latter sets in with its usual symptoms.

As a result of the association of arteriosclerosis in other areas in those patients of rather advanced age, arterial symptoms form a prominent part of the clinical history.

(3) The general condition is good. "These patients are usually of ruddy complexion, stocky build, plethoric habits, active temperament, live men and women" (Meara). Still, here, exceptions may occur.

(4) There is high blood-pressure; at first these may consist of transitory rises.

(5) The heart is markedly hypertrophied, at first involving chiefly the left ventricle, when it may be difficult of demonstration by physical signs, although teleorentgenograms or orthodiagrams always show the hypertrophy of the so-called sock heart. With the onset of decompensation dilatation sets in with enlargement of the heart to the right and left.

(6) The blood rarely ever shows an anemia; indeed there is frequently a marked polycythemia—a valuable distinction from the end stage of chronic diffuse glomerulonephritis and the combination form.

(7) The urine often shows no abnormality at all, not infrequently a trace of albumin and a few casts; often there is nycturia and a moderate night polyuria, the cardiac origin of which is readily recognized by the accompanying day oliguria.

(8) The eye-ground changes are those of arteriosclerosis, never those of chronic nephritis. The presence of papillitis and neuroretinitis is conclusive evidence that the case has passed into the combination form.

(9) The kidney function is unimpaired. It excretes water as usual. It concentrates normally; phthalein excretion is good; there is no increase in the blood urea and non-protein nitrogen. There are conflicting views with respect to salt excretion which need further study.

(10) The form of uremia, so called, which is characteristic of this form of disease is that in which eclamptic equivalents occur, such symptom as headaches, dizziness, Cheyne-Stokes' respiration, nocturnal asthma, cerebral crises, transitory aphasia and paralysis, increased reflexes, physical disturbances, etc. Eclamptic uremia may rarely occur, true uremia with azotemia is regularly absent.

Treatment.—So little is known of the real cause and pathogenesis of arteriosclerosis of the small and smallest blood-vessels of the kidney that but little can be done in the way of prophylaxis. Especially those who are hereditarily disposed should avoid strain both physical and mental and should guard against infection, endogenous and exogenous intoxications and metabolic diseases.

In the management of benign hypertension it is well to realize what may be accomplished in the way of treatment—that the early cases may be cured, the more advanced arrested and many of the severe symptoms in the late stages palliated. These results may be accomplished by: the judicious application of psychotherapy; regulation of the diet; sane advice as to work, rest, exercise and vacation; the careful use of hydro-, mechanico- and electrotherapy; the proper use of drugs; control of infections; and the application of certain surgical procedures.

PSYCHOTHERAPY.—It is desirable to dispel fear where this can honestly be done; it is absolutely necessary to inspire the patient with confidence and hope; and he should be encouraged to lead a hygienic life and cultivate equanimity. To accomplish these things it is necessary to know the minutest details of the patient's habits, to make a most careful investigation of the case, to impress upon him the nature of the illness, to convince him that he will have the doctor's best efforts to do the best thing for him, and to set him right on the significance of a high blood-pressure. He should be made to realize that with care and perseverance the early case can be cured. He may have to change entirely his mode of life, but the results obtained will make this worth while. Even in an advanced case he may be kept in functional activity of both body and mind and even in the last stages much may be done in the way of palliation.

He must be taught that the dangers of the disease are to be expected, chiefly from the failure of the heart and a vascular accident, that the high blood-pressure is a compensatory process to meet the demands made on the cardiovascular system and needs not to be treated as such. Only if danger of apoplexy or hemorrhage into other important organs threaten should especial measures be instituted to reduce it.

DIET.—As there is no impairment of the kidney function, no especial restriction as to the proteins is necessary. It must ever be kept in mind that the patient's nutrition must be maintained and an effort made to give such quantity of food as will keep his weight just below his ideal, calculated standard. The proper balance of diet must be considered. In a general way, the patient may be advised to let his diet consist chiefly of bread, milk and vegetables, with a small piece of meat once a day. He should especially avoid large quantities of meat, meat broths, spices, alcohols, acids and an excessive quantity of salt. Due consideration should be given to the patient's tastes and power of digestion.

The motto of the hypertonic should be "To avoid hurry and worry." Both physical and mental strain in this condition predispose to the development of cardiac insufficiency and cerebral hemorrhage. In the early stages of the disease the patient's occupation need not be given up. If, however, it has entailed great haste and worry, the patient must be urged to slow down. Shorten the hours of work, take more vacations, indulge in pleasant recreation, not forgetting, however, that in the latter, excesses may easily be reached. Good advice for these patients, is that any exercise which produces undue shortness of breath, is too much.

HYDRO-, MECHANICO-, AND ELECTROTHERAPY.—The author has obtained the impression that these forms of therapy are often overdone with hypertonic patients. In the first stages of the disease the bathing habits may be those of an ordinary healthy person. In the later stages, the baths should be neither hot nor cold, but warm or tepid. Here especially should violent forms of hydrotherapy and mechanotherapy be avoided. A yearly visit to a Spa where these forms of treatment are not carried

to excess is often beneficial. Massage may be of advantage in those cases where periods of enforced rest are necessary.

The application of high frequency currents in cases of benign hypertension has been highly praised by some, but the author's impression from observation is that they, as other forms of electrotherapeutics, have little value other than that of a psychic nature.

While it is true that a dry, equable climate is best suited for the hypertensive patients, it is possible by protection—proper clothing, the avoidance of chilling and exposure to inclement weather—to get along very well in any place in which circumstances may place one.

Drugs have a place in the treatment of benign hypertension. If constipation exists, an effort should be made to overcome this by diet, exercise, and habits, and when necessary, **mineral oil** and a **gentle laxative** may be given by night, supplemented by **mild salines** in the morning. In any event a dose of **blue mass** combined with **euonymin** and **extract of Hyoscyamus** (*masse Hydrargyrii*, grains 10 [.65 gram], euonymin, grains 3 [.195 gram], extractum Hyoscyami, grain $\frac{1}{2}$ [.0324 gram], in capsule) may be taken at bed time once every week or two with advantage.

Small doses of **iodids** over a long period of time with regular interruptions may be of advantage, but it should not be forgotten that patients who have a tendency to hyperthyroidism, emaciation and severe headaches do not bear iodids well. They should not of course be used in those patients who present a special idiosyncrasy against them. The vasodilators—**nitrites**, **nitroglycerin**, **erythrol tetranitrate**—are of but little advantage except in those cases associated with angina pectoris or threatened cerebral apoplexy.

In the early and moderately advanced stages of benign hypertension all definite foci of infection, as in the tonsils, paranasal sinuses, teeth, chronic cholecystitis, chronic appendicitis, chronic prostatitis should receive the appropriate surgical treatment. In the later stages, however, great care should be exercised not to subject the patient to unnecessary surgical procedures, or to such as may result more seriously to the patient than the condition for which they are undertaken.

Such complications as myocardial insufficiency and eclamptic equivalents have been fully discussed in the sections on circulatory nephropathies and uremia (*q.v.*).

In cases complicated by angina pectoris, those things which are found to bring on the pain—exercise, indiscretions in diet, tobacco, etc.,—should be avoided and nitroglycerin or the nitrites administered both during the attack and in the intervals.

Complicating infections should receive prompt and appropriate treatment.

Prognosis.—In its early stages benign hypertension is a curable disease. In more advanced stages its progress may be arrested or delayed, while in the most advanced stages many of its symptoms may for a long time be ameliorated.

The dangers are first from the heart, second from the arteries and

third from pulmonary complications. In 86 cases of death from the disease, Volhard and Fahr noted 7 from intercurrent disease, 51 from cardiac insufficiency (10 of which were associated with bronchopneumonia), 18 from cerebral arteriosclerosis (11 softening, 5 hemorrhage, and 2 suicide), 10 from bronchopneumonia and 3 from lobar pneumonia. Not one of these cases resulted in death because of kidney insufficiency.

Pathology.—**THE KIDNEY.**—*Macroscopical.*—The gross appearance of the kidney varies greatly according to the size of the vessels involved and the extent of the arteriosclerotic process. In 89 cases of Volhard and Fahr which came to autopsy, 37 showed contracted kidneys and 52 noncontracted kidneys. The appearance of the contracted kidney will depend upon the distribution of the arteriosclerosis. If the larger vessels are involved, a more or less unevenness of the kidney will result; if the small vessels, a fine granulation. With diffuse involvement of the smaller vessels, the granulations differ from those in the end stage of chronic diffuse glomerulonephritis. In the latter, the islands of widened and hypertrophied tubules are responsible for the granulation, while in the former the granulations are produced by scarring retractions between which the parenchyma is intact.

The primary contracted kidney is greatly diminished in size, the capsule is adherent, the outer surface is finely granular and red. On cut surface, the cortex markedly thinned and red in color, the cortical markings are preserved and the cortex and pyramids are well differentiated from each other. There is a marked tendency to the formation of small cysts.

In the noncontracted kidneys of benign hypertension, which are apparently of more frequent occurrence, the size is not diminished, but may be enlarged as the result of chronic passive congestion.

It is brownish red in color and the consistency is firm. The cortical markings are preserved and the cortex is differentiated from the pyramids. Many of these kidneys without careful microscopic examination would possibly be reported as normal.

Ziegler's findings with respect to arteriosclerosis have been confirmed by subsequent observers. The arteriosclerosis of the vessels produces disturbances in nutrition which occur focally and lead to degeneration of larger or smaller areas of the kidney. The areas of degeneration are replaced by wedge-shaped areas of connective tissue in which the glomeruli are destroyed. Jores believed that, due to the frequent involvement of the vasa afferentia, the glomerulus is destroyed as a whole. Fahr, however, states that by serial sections, the various steps of the destruction may be seen and that a part of the capillary loops may be destroyed. Those tubules belonging to the destroyed glomeruli also undergo destruction. Those which are preserved may contain hyalin casts. The portions of the parenchyma whose blood supply is not involved in the arteriosclerotic process is intact.

The changes in the small vessels consist of hyperplastic intimal thickening which by some is called the stage of presclerosis, and regressive changes which are designated arteriosclerosis.

The heart is regularly hypertrophied and usually reaches an extreme degree. Among 128 cases, Fahr classified the kidneys according to the extent of the vascular changes. In Group I were placed those cases in which all sections showed considerable arteriosclerotic changes not only in the medium and large vessels, but more or less pronounced changes in the small vessels (interlobular and afferentiæ). In Group II were placed such as showed distinct changes in medium-sized vessels, but also found here and there in the small vessels, though much less marked than in Group I.

In Group III changes are completely lacking in the small vessels (afferentiæ and interlobular); in the medium-sized vessels (arciformes and larger branches of the interlobular), hyperplastic intimal thickening with sometimes transition to arteriosclerosis is present, but often slight or completely absent.

In Group I (41 cases) heart hypertrophy was present 34 times. In 13 cases the heart weight exceeded 400 grams (.88 lb.); in 21, the weight was between 300 and 400 grams. Cardiac hypertrophy was absent in seven cases.

In Group II (45 cases), heart hypertrophy was present in 51 cases. In 12, the heart weight exceeded 400 grams; in 19, the weight was between 300 and 400 grams. There was no hypertrophy in 14 cases.

In Group III heart hypertrophy was lacking throughout.

There are different views with respect to the cause of heart hypertrophy and increased blood-pressure in these cases. Two possibilities have been chiefly discussed: (1) arteriosclerosis of the small blood-vessels, especially those of the kidney produce the hypertension and cardiac hypertrophy; (2) some cause, either intra- or extrarenal in origin, tends to produce increased blood-pressure, and this, on the one hand, leads to changes in the small blood-vessels and on the other, to hypertrophy of the heart.

Fahr accepts the mechanical theory, and after discussing the objections raised to this view by Ludwig, Senator and Katzenstein, concludes that the most important cause for the origin of the increased blood-pressure and heart hypertrophy must be sought in the arteriosclerosis of the small vessels. Other organs, especially the pancreas, spleen and brain, may come into consideration, but the arteriosclerotic changes of the small vessels of the kidney occupy the chief place.

Jores states: "For some reason still unknown, the cardiac hypertrophy connected with the primary contracted kidney is more advanced than that associated with any other form of Bright's disease. Investigating this question, I found that the degree of cardiac hypertrophy can depend neither upon the variety nor the severity of the renal lesion; furthermore, the enlargement is present while changes in the kidney are still insignificant. I, therefore, consider it possible, nay, even probable, that in the case of the primary contracted kidney, the heightened blood-pressure is not produced, or at least not solely produced, by the condition in the kidney, but rather by extrarenal causes. This being true, a primarily heightened blood-pressure would have to be regarded as the

basic condition responsible for both the cardiac and the renal lesion (Frank), or, as I have expressed it, it would have to be assumed that the noxa which causes the contracted kidney induces, from the first, an augmentation of blood-pressure."

Among the changes found throughout the remainder of the body in connection with benign hypertension are such consequences of arteriosclerosis as cerebral hemorrhage and necrosis of the myocardium, which supervenes only rarely and as a result of extensive disease in the coronary arteries.

ILLUSTRATIVE CASE No. I.—J. L. M., male, age 44, married, wholesale furniture dealer. Observed November 3, 1920.

Chief Complaint.—Spitting blood for the past two or three days.

Family History.—Father, alive and well; mother, alive and well; 8 sibs, 7 alive and well, 1 dead, cause unknown.

Past History.—Measles, whooping-cough, pneumonia in childhood. Has never been sick since grown. He has been very actively engaged in business for the last twenty years without a vacation. Under great physical and mental strain.

Present Illness.—On the night of November 1, 1920, he felt as if he wanted to expectorate. When he did, he brought up about one teaspoonful of bright red blood. The sputum the next day was streaked with blood. To-day it is clear. The patient has not felt as if he has had any fever; he lost no weight and feels well.

Physical Examination.—The patient's weight is 167 lbs. His average weight is 160 lbs. Temperature 98.2° F. (36.77° C.). Pulse 72, blood-pressure 180–120. The tonsils are enlarged and ragged and he has recently had an abscessed tooth. There is no adenopathy. The chest moves full and equally. There is nowhere any abnormality to palpation, percussion or auscultation. The heart is enlarged, the apex being in the sixth interspace outside the midclavicular line. The rhythm is normal, the sounds are clear and the aortic sound is markedly accentuated. The abdomen and nervous system are without abnormal findings.

The temperature takings at 8, 12, 4, and 8 daily for five days did not show any increase above normal. The blood-pressure on November 6, in the afternoon, was 182–120.

Urine.—Specific gravity 1014; acid, no albumin, no sugar, no casts.

Blood.—Hemoglobin 100 per cent. (Sahli); red cells 5,020,000; leukocytes 8,200; polymorphonuclears 65 per cent.; small lymphocytes 21 per cent.; large mononuclears 11 per cent.; and basophils 3 per cent. Wassermann was negative. Examination of specimen of sputum obtained on four separate days was negative for tubercle bacilli.

Special Examination.—X-ray (stereoscopic plates) shows peribronchial thickening over both lungs, a calcified area in the left lung about the area of the seventh rib. Thickening more marked in the lower lobes. The hili are thickened. There is an area of infiltration at apex of left lung level of the third rib.

Nose and Throat.—The tonsils are infected. There is free blood on the vocal chords; there is no evidence of thickening or ulceration.

Modified Mosenthal.—Ordinary diet with all fluids taken at meal times.

URINE REACTION TO MOSENTHAL TEST

Time	Quantity	Specific Gravity	Water	Blood Urea	Creatinin
10 A. M.	78 c.c.	1018			
12 M.	91 c.c.	1016			
2 P. M.	185 c.c.	1010			
4 P. M.	120 c.c.	1010			
6 P. M.	70 c.c.	1018			
8 P. M.	70 c.c.	1020			
Total day	614 c.c.	1016	1721 c.c.	28.5 mg. per 100. c.c.	1.6 mg. per 100 c.c.
Total night	577 c.c.				
Total 24 hrs.	1191 c.c.				

Clinical Diagnosis.—Focal infection tonsils and teeth, hemoptysis slight, and benign hypertension.

ILLUSTRATIVE CASE NO. II.—Mrs. A. H. M., consulted the author at office, May 18, 1921. Female, 47 years of age, married, housewife.

Chief Complaint.—Periodical attacks of dizziness during which she is unable to stand. Duration 3 months.

Family History.—Father, alive and well; mother, died of Bright's disease; 6 sibs, 5 alive and well; 1 died in infancy.

Past History.—Measles, pertussis, malaria and bronchopneumonia in childhood. Had a nervous breakdown at the age of 22.

Menstrual History.—Menstruation began at 15 years of age. It was always regular, until menopause which occurred 5 years ago. She has had no pregnancies. Married 30 years.

Present Illness.—About five months ago awoke one morning feeling quite dizzy, accompanied by nausea. She took purgatives, but they gave no relief. The attacks have come irregularly since that time, sometimes accompanied by nausea, but not always. The patient remained in bed for two months, but the dizziness was not improved.

She thinks she has lost about 10 pounds in weight during this time. The appetite is variable and occasionally there is a pain radiating along the left costal border. She has become very weak. Symptoms referable to the urinary system are negative. She has no cramping sensations, but is annoyed by a buzzing noise in the ears, particularly the left.

Physical Examinations.—The patient, a lady, is slightly undernourished, 16 lbs. underweight; the skin is subicteric and the mucous membranes are pale. Temperature 99.4° F. (37.44° C.), pulse 124 per

minute, blood-pressure, 190-110. The *tongue* is large with indentations in the margin; there is much dental work, mostly fillings; the *teeth* are not sensitive and the gums are in good condition. The *throat* is negative. The posterior cervical glands (left) and submental glands are slightly enlarged. The *thyroid* is barely palpable, not granular nor vascular. The patient is a little hoarse. *Chest*: The respiratory movements are full and equal on both sides. The vocal fremitus is slightly diminished at left apex. The respiratory murmur is clear throughout both sides of the chest. *Heart*: The apex beat is in the sixth interspace outside the midclavicular line, there is marked tachycardia and accentuation of the aortic second sound; the heart is, otherwise, negative. *Abdomen*: No masses or areas of tenderness. It presents the visceroptotic habitus and right kidney is movable (second degree). *Nervous System*: Von Graefe positive; Dalrymple slightly positive; Stellwag negative; Möbius negative; Jellinek positive; Rosenbach positive. There is slight nystagmus on looking upward, none to the right or left. Finger to nose test imperfect. Pass points on the right o.k., two inches to the right on the left side. The deep reflexes are active, the superficial normal. Dermographia is present. There is very slight exophthalmos, and a fine tremor of the outstretched hand.

Laboratory Findings.—*Urine*.—Light yellow, specific gravity 1010, acid, albumin and sugar negative. Microscopically, epithelium, a few mucous shreds—no casts. *Blood*: Polymorphonuclears 56 per cent.; small lymphocytes 37 per cent.; large mononuclears 5 per cent.; basophils 2 per cent. The red cells are normal in size and in staining reaction. Wassermann, negative. *Gastric Contents*: Dock test breakfast; removed after 45 minutes, 20 c.c., dark brown, a large quantity of mucus. Free blood present, free HCl 8; total acidity 58.

Special Examinations.—Basal metabolism (Jones' Metabolimeter). Age 47; height 61.5 ins.; pulse 126; patient was not excited and breathed quietly; weight 101 lbs.; first liter of oxygen, 5.2 min.; second liter of oxygen, 5 min.; basal metabolic rate—8.

X-ray of Stomach.—Meal 4 ounces of barium; 1st plate, 10 minutes after meal; 2nd plate, 15 minutes after meal; and 3rd plate, 4 hours after meal. The stomach is ptosed, shows no deformities, is well formed. Duodenal caps shows deformity. There is a moderate four-hour residue. Impression duodenal ulcer. *Barany Tests*: Show toxic labyrinthitis. The left practically destroyed. The blood urea was 31.5 mg. per 100 c.c.

Clinical Diagnosis.—Benign hypertension, toxic labyrinthitis, and duodenal ulcer.

Treatment.—Sippy régime for duodenal ulcer, the avoidance of hurry and worry. The patient returned September 13, 1921. She feels a great deal better, she says practically well; she has gained 16 lbs., her ideal calculated weight, but is at times still dizzy. The blood-pressure is 200-100, the urine contains neither albumin nor casts and the blood urea is 33 mg. per 100 c.c.

ILLUSTRATIVE CASE No. III.—M. G. R. K., male, age 38, married, railroad agent. Seen at office, March 4, 1921.

Chief Complaint.—Paralysis of the right side of the body, February 9, 1921.

Family History.—Father, died of pneumonia; mother, died of apoplexy; one sib, alive and well.

Past History.—Typhoid in childhood; malaria 16 years ago. Tripper and lues denied. Up to several years ago, used alcoholic beverages to excess. Wassermann in July, 1920, was negative.

Present Illness.—On February 9, 1921, while in a fit of anger, the patient felt a burning sensation in the left side of the face, the tongue became thick and the speech was impaired. The left side of the face and the tongue became paralyzed. There was no loss of consciousness. At this time there was a feeling of weakness in the right arm and leg, but he was not completely paralyzed until the next day, i.e., the right arm was completely paralyzed but he was able to move the leg slightly. In about a week the arm began to improve and has gradually improved ever since. He feels very well now.

Physical Examination.—Well-nourished gentleman, 170 lbs., 5 ft., 9½ ins. in height, about 10 lbs. over his calculated ideal weight. Left eye out, result of an injury several years ago. Right pupil dilated, reacts to light. Residual paralysis of the left facial. Teeth, pyorrhea; throat red. Temperature 98° F. (36.66° C.). Pulse 84 per minute. Blood-pressure 190–120. The lungs are negative. The heart is slightly hypertrophied; there is no evidence of decompensation. There is residual paralysis of the right side of the body. Right patellar markedly increased; Babinski positive on the right.

Laboratory Findings.—**Urine.**—Cloudy, yellow, specific gravity 1016; acid in reaction, albumin and sugar negative. Microscopically, a rare red blood-cell is shown; no casts. **Blood:** Polymorphonuclears 67 per cent.; small lymphocytes 37 per cent.; large mononuclears 6 per cent.; red cells, normal as to size, shape and staining reactions. Wassermann—negative. **Kidney Function:** Phthalein 65 per cent. in 2 hours and 10 min. Blood urea 21 mg. per 100 c.c.

Clinical Diagnosis.—Benign hypertension, and crossed hemiplegia.

ILLUSTRATIVE CASE No. IV.—Mrs. W. A. S., age 62, married, housewife. Seen first at office, October 31, 1919.

Chief Complaint.—Pain left side of chest for two or three days.

Family History.—Father died of stomach trouble; mother, of gall-bladder disease; 7 sibs; one brother died of paralysis; one sister suffers from high blood-pressure.

Past History.—Had typhoid fever in 1896. Pneumonia. Gall-bladder diseases, colic, and passed gall-stones 15 years ago.

Marital History.—Five children; menopause 10 years ago.

Present Illness.—About two weeks ago had general aching which was intense. Had been under a severe strain as a result of brother's illness.

A few days ago had an attack of severe pain in the left side with temperature of 101° F. (38.33° C.). The pain was relieved in about three days. Has had no fever since. The throat was sore at this time. The patient still complains of weakness and nervousness. About 4 A. M. Wednesday, she had a collapse, weak and irregular pulse. This was relieved by aromatic spirits of ammonia and hot water. She has had a great deal of cold, clammy perspiration. Has shortness of breath on exercise for the last three years. Her feet swell slightly at times. Her digestion is very good. Gets up several times at night to void bladder. She passes a "large quantity of urine as clear as spring water." She is very nervous—tremor, paresthesias,—and is easily upset.

Physical Examination.—She is well nourished, over weight. Temperature 99° F. (37.22° C.); pulse 96 per minute; blood-pressure 220–120. The teeth are very bad. The throat is red. There is a pleuritic friction rub in the left lower axilla. The heart is hypertrophied. The apex is in the sixth intercostal space outside the midclavicular line. The aortic second is markedly accentuated. The abdomen and nervous systems are without abnormal findings. The urine was clear, specific gravity 1015, albumin present, no sugar; microscopically, an occasional hyalin cast. The blood showed no evidence of anemia. The phenolsulphonephthalein output was 84 per cent. in 2 hours and 10 minutes.

Diagnosis.—Benign hypertension, and fibrinous pleurisy.

Treatment.—The patient was talked to frankly as to her condition, advised to avoid hurry and worry; to let her diet consist chiefly of milk and vegetables with a small piece of meat once a day; to take a mercurial purge once every week or two, etc. She returned July 27, 1920, and went into the hospital for a few days. She had felt much better until recently; she thinks she had taken more exercise and eaten more than she should. Her general condition was about the same. Blood-pressure 210–110. The symptoms of relative myocardial insufficiency had been much better, but recently she had been quite short of breath on exercise.

The patient was kept in bed for two weeks, given an O'Hare diet sheet with a score of 15 for one week, and after that of 20; fluids limited to 1500 c.c. per day. She returned June 20, 1921. Her teeth had been extracted, and she was feeling very well indeed. Temperature normal, pulse 96, blood-pressure 210–130. The apex beat was in the sixth interspace just outside the midclavicular line. There was no evidence of stasis anywhere. *Urine:* Cloudy, yellow, specific gravity, 1016, acid, albumin and sugar negative; microscopically hyalin casts, pus cells + +, and epithelial cells + + +. *Blood:* Red cells 5,250,000; hemoglobin 100 per cent. (Sahli); white cells, 6,500; polymorphonuclears 66 per cent.; small lymphocytes 20 per cent.; large mononuclears 13 per cent.; basophils 1 per cent. *Blood Urea:* 39 mg. per 100 c.c. *Creatinin:* 2.09 mg. per 100 c.c.

Functional Tests.—July 27 to 30, 1920, at rest in bed, on an ordinary diet, with the total intake of fluids at meal times.

MOSENTHAL TEST

Time	Quantity	Specific Gravity	NaCl		Nitrogen	
			Per cent.	Grams	Per cent.	Grams
8-10 A. M.	22 c.c.	1020				
10 A. M.-12 M.	155 c.c.	1015				
12 M.-2 P. M.	90 c.c.	1017				
2-4 P. M.	70 c.c.	1021				
4-6 P. M.	55 c.c.	1025				
6-8 P. M.	65 c.c.	1029				
Total day	457 c.c.		1.08	4.58	.608	2.39
Total night	610 c.c.	1018	1.095	8.82	.546	3.22
Total 24 hrs.	1067 c.c.			13.40		5.61
Intake	1720 c.c. (fluid)			8		13
Phenolsulpho-nephthalein output	15 per cent. in 2 hrs., 10 mins.					
Blood urea	62 mg. per 100 c.c.					
Creatinin	1.9 mg. per 100 c.c.					

The patient returned on October 28, 1921. She had spent the summer on the Gulf Coast and had progressed nicely. At this time her blood-pressure was 200-120. *Urine*: Pale, yellow, specific gravity 1015, acid, albumin—a trace. Sugar—negative. Microscopically no casts. *Blood Urea*: 41 mg. per 100 c.c.

MALIGNANT HYPERTENSION

(Combination Form of Hypertension, Sclerosis Plus Nephritis, Genuine Contracted Kidney with Tendency to Kidney Insufficiency)

As many times stated, the malignant form of hypertension includes sclerosis of the small and smallest blood-vessels of the kidney combined with gradual and progressive chronic glomerulonephritis. The sclerosis with complicated acute nephritis is not included.

Etiology.—The etiology of the arteriosclerosis of the kidney vessels is the same, as far as known, as that of benign hypertension. The cause of the superimposed degeneration and inflammatory lesions of the glomeruli is as little known as that of arteriosclerosis. Volhard has discussed two possibilities: (1) That these changes are due to an unknown physiologic product of metabolism which acts toxically on an arteriosclerotic basis; and (2) that they are due to an abnormal path-

ological product of metabolism which also causes marked involvement of the vessels in the arteriosclerotic process.

There are several facts which are opposed to the latter view: (1) Not infrequently the small and smallest blood-vessels of the kidney show arteriosclerotic changes in benign hypertension; (2) the inflammatory process occurs at all stages of the arteriosclerotic process—in the early as well as late cases; (3) occasionally a previous stage of benign hypertension is observed; (4) both conditions attack patients of the same age; (5) there is great similarity of the symptoms in both.

For these reasons Volhard is inclined to accept the possibility that the cause may be found in some physiologic product of metabolism which acts on an arteriosclerotic basis. The age and sex distribution may be seen in the following table:

Volhard and Fahr's Cases			Author's Cases	
Age	Male	Female	Male	Female
30-40	6
41-50	8	3	3	1
51-60	13	2	5	1
61-70	2	1	7	3
71-76	1	..	1	1
	30	6	16	6

In Volhard and Fahr's cases, there was a history of lead poisoning in 4; use of tobacco in 5; alcohol in 2; and typical gout in 3.

Symptomatology.—The onset is gradual. Usually benign hypertension has existed for several years before the nephritis manifests itself clinically in the impaired kidney function. Albuminuric retinitis is sometimes an early sign. It may develop before the inflammatory changes can be detected.

The symptoms with reference to the cardiovascular system are the same as those in benign hypertension. They all, however, tend to be more severe. The relative myocardial insufficiency which tends to remain stationary in benign hypertension here soon passes over into complete decompensation. Attacks of angina pectoris are more frequent. The nocturnal attacks of asthma pass over into pronounced edema of the lungs, which is associated with anginoid complaints, a feeling of constriction in the chest, etc.

The arterial symptoms of benign hypertension are also encountered in the combination form. The gross cerebral accidents—cerebral hemorrhage—are probably less frequent, but symptoms due to hemorrhages or softening, such as transitory aphasia, temporary facial paresis or hemiparesis with short-continuing paralysis without loss of consciousness, fainting and dizzy attacks with following deafness, astereognosis,

mental blindness, etc., occur more frequently. Cheyne-Stokes' breathing is very frequently observed.

Psychical symptoms are much more apt to occur and to be more severe in the combination form. These may partake of an irritating or depressing nature. They may so dominate the picture as to obscure the renal-arterial nature of the disease. The patient may be nervous, irritable, unruly or violent; or melancholic, whiney, and quick to cry. They are filled with fears of death and live between hope and fear. They are critical, dissatisfied with everything and resist the orders of the physicians and nurses. Mental weakness becomes noticeable and they degenerate mentally very rapidly. Inability to concentrate is often complained of, fatigue is marked, comprehension is slow and drowsiness comes on.

Usually these symptoms come on slowly, but confused conditions, wandering ideas and hallucinations may come on quickly. They may suddenly become violent and disorientated as to time and place. These conditions are sometimes mistaken for general paresis.

The patients suffer from headache of a migrainous type and severe occipital headaches, the former probably an eclamptic equivalent, and the latter due to increased intracerebral pressure. Eclamptic uremia may also occur, though true uremia with azotemia is more frequent, and the certain end if not produced by vascular accident, myocardial insufficiency or terminal infection.

PHYSICAL FINDINGS.—General Appearance.—In contradistinction to benign hypertension the general appearance and strength suffers early. Emaciation is quite marked and there may be a cachectic appearance as in the end stage of chronic diffuse glomerulonephritis. This may be found in early cases before the inflammatory and degenerative changes in the kidney have progressed very far. The skin assumes a rather characteristic grayish yellow color. There is not infrequently slight exophthalmos giving the face a Basedowan expression, which is that of a sick person. The least effort exhausts the patient.

Blood-pressure.—The highest values are observed in the malignant form, and as a rule they are persistently high, but showing the tendency to transitory rises as in benign hypertension.

Blood-pressure	Volhard and Fahr's Cases	Authors' Cases
Below 170 mm. Hg.	1	4
170–180 mm. Hg.	2	4
180–199 mm. Hg.	5	2
200–219 mm. Hg.	6	3
220–239 mm. Hg.	9	4
240–259 mm. Hg.	9	1
260–280 mm. Hg.	4	1
	36	19

The Heart.—The largest hearts are also found in this form of nephropathy. Volhard and Fahr found the largest heart weighing 1000 grams (2.2 lbs.). The average weight of 10 cases was 732 grams, against 570 grams in benign sclerosis in the male sex.

The clinical manifestations of enlargement are manifest. The apex is displaced downward and outward, is heaving in character; the aortic second is accentuated as are the sounds at the other ostia. Both presystolic and diastolic gallop rhythm may be encountered. All of the signs which are found in benign hypertension are also found here. There is possibly a greater tendency to arrhythmia. Cardiac edema is often present, but renal edema as in the benign form is absent.

LABORATORY FINDINGS.—Urine.—The urine presents quite a variable picture, depending largely upon the stage to which the superimposed nephritis has developed. In the early stage the color and quantity of the urine may be normal, except an abnormal variation between the day and night urine. With myocardial insufficiency the quantity decreases and the color and concentration increases. With the preservation of the heart strength and the progress of the nephritis the quantity increases both day and night with a fixed specific gravity, just as in the end stage of chronic diffuse glomerulonephritis. Often these changes in the urine may be followed while the case is under observation.

Albuminuria.—In the early cases it may be absent, but it soon appears and tends to be present in somewhat greater quantity than in benign hypertension. It may increase markedly as the result of chronic passive congestion of the kidney. It was absent in 3 of the author's cases, + in 15, ++ in 1, and +++ in 1. *Sediment:* Casts are almost regularly found; they may be of all varieties. Leukocytes are regularly present, also epithelium, occasionally lipoids, and more rarely red blood-cells. *Blood:* In contrast to benign hypertension the blood constantly shows a secondary anemia which varies greatly in degree.

SPECIAL EXAMINATION.—Ophthalmoscopic.—Changes in the eye-grounds are the rule. As stated above, it may sometimes occur before there is evidence from the urine and other sources that nephritis is in progress. Neuroretinitis albuminurica is of course the change here referred to, but the arteriosclerotic changes described under benign hypertension may occur here.

Functional Kidney Tests.—These vary greatly, but they are usually impaired, this forming one of the pathognomonic signs of the malignant form. One of the earliest signs of kidney insufficiency is a night polyuria with a low specific gravity. With the progress of the disease, the modified Mosenthal test shows a day polyuria, fixed specific gravity, and low concentration of the salt and nitrogen of both the day and night urine. The phenolsulphonephthalein output is low, varying from the lower limits of normal to 0, in 2 hours and 10 minutes. In 7 of the author's cases in which it was estimated, the values were 26, 6, 3, 39, 8, 3, 5, and 0 per cent.

There is regularly nitrogen retention. The blood urea in 19 cases

was: 55.2, 52.5, 99.4, 58.5, 55.5, 53, 75, 61.5, 75, 67.5, 64.5, 122.5, 80, 88.6, 96.45, 153.75, 124.9, 68.2, and 321 mg. per 100 c.c. of blood.

The same factors which affect the variation of the kidney function in chronic diffuse glomerulonephritis in the end stage also operate here. What was said there with respect to acidosis and the basal metabolic rate also obtains here.

Diagnostic Features.—(1) Occurs most frequently from 40 to 50 years of age and in men.

(2) The good general condition of benign hypertension rapidly declines and soon presents the characteristic cachectic condition of chronic nephritis.

(3) The disease runs its course as a cardiovascular renal disease. The cardiovascular symptoms as compared with benign hypertension and characterized by a tendency to greater severity.

(4) The blood-pressure is high and constantly maintained, showing the highest values.

(5) Cardiac hypertrophy is marked, comes on early and here we find the largest hearts.

(6) Edema when present is of cardiac origin.

(7) The blood shows marked secondary anemia in contrast to benign hypertension.

(8) The urine shows nycturia, a day and night polyuria, a low specific gravity, albumin, and cylindruria of moderate grades.

(9) Papillitis and neuroretinitis are the rule and are certain indications that the case does not belong to the type of benign hypertension, although the kidney functional tests may show little or no impairment.

(10) Impairment of kidney function is the chief characteristic of this type. This varies from the slightest to the most severe.

(11) If death does not occur earlier from the cardiovascular component of the disease or from a terminal infection, the end results from true uremia as in the end stage of chronic diffuse glomerulonephritis. Eclamptic equivalents are prominent as in benign hypertension, the psychical symptoms tending to be more severe. Eclamptic uremia rarely occurs.

Treatment.—Little more need be said of the treatment of the combination form than has been fully discussed in the treatment of benign hypertension and the various stages of kidney insufficiency in the section on the end stage of chronic diffuse glomerulonephritis (*q.v.*).

Prognosis.—The gradual nephritis of unknown etiology which attacks a previously arteriosclerotic kidney is in spite of timely treatment always an incurable disease and of unfavorable prognosis. If death does not occur earlier from myocardial insufficiency, a vascular accident or terminal infection, uremia is the certain outcome. A few months may decide this. After the nephritic component becomes decidedly manifest, the course rarely extends over more than a year or two.

Pathology.—**MACROSCOPICAL.**—The kidneys, as in benign hypertension, may be contracted or noncontracted, though in malignant hypertension the former is more frequent.

Of 23 cases coming to autopsy, Volhard and Fahr found the kidneys noncontracted in 7 cases, and contracted in 16 cases. In contrast to the noncontracted kidney of benign hypertension, the cortical markings are completely obscured; the limit between cortex and medulla is indistinct. The cortex is beset with numerous yellowish, smutty flecks and streaks. The outer surface often shows only a suggestion of flat granulation and is flecked with yellow brownish spots. The consistency is tough throughout, and on section the vessels stand open. In the contracted form, the outer surface shows regular, tolerably fine granulations which are grayish yellow in color. The interlying parenchyma is of a brown color. These conform to the red granular kidney of Jores; except in the pure arteriosclerotic form the cortical markings are recognizable.

MICROSCOPICAL.—The glomeruli in the atrophic areas undergo degeneration, as in the arteriosclerotic form, but these are more numerous and show much richer round cell infiltration. In the glomeruli there are also degenerative changes and occasionally a true inflammatory process.

The epithelium also shows fatty changes; fat droplets occur which run together to form large drops. Some of the fat crystals are singly retracting; but some doubly retracting crystals may be found. Also changes may be seen in the glomeruli which resemble the hyalin droplet degeneration of the tubular epithelium. Besides these degenerative changes other glomeruli show inflammatory changes; there may be small collections of leukocytes and in places the layers of the capsule may be adherent, while still other loops may contain fibrin and occasional red blood-cells.

Sometimes the inflammatory changes in the intracapsular space may assume the half-moon shape. Occasionally one sees the vasa afferentia, leading to the inflamed glomerulus, markedly changed by arteriosclerosis. The inflammatory changes in the glomeruli vary very much in intensity from case to case. The greater number of glomeruli in a section is free from inflammatory changes.

Fatty changes in variable intensity may be seen in the parenchyma; not rarely there are considerable accumulations of fat and double refracting substances in the interstitium, as well as dropsical degeneration in the epithelium of the convoluted tubules.

The changes in the vascular system are analogous to those described for arteriosclerosis except the small and smallest blood-vessels are more intensive and extensive.

The heart is markedly hypertrophied, as stated above, showing the weights greater than in any other nephropathy. Sclerosis of the coronary arteria is frequently found. This occurred in 14 of 23 cases of Volhard and Fahr. Other areas may be involved in the arteriosclerotic process, as in benign hypertension.

ILLUSTRATIVE CASE NO. I.—J. E. H., male, white, age 50, married, chemist. Seen first at his residence, July 5, 1921.

Chief Complaint.—Severe pain in the abdomen.

Family History.—Father died of angina pectoris; mother is alive and has pernicious anemia; 5 sibs, 4 alive and well; 1 died of diphtheria.

Past History.—In childhood had measles, scarlet fever, much tonsillitis, tonsillectomy. Post childhood, as a young man had a great deal of malaria, nervous prostration 17 years ago. For the past 15 years, while he has not been confined to bed, has had a good deal of indisposition. He states that his urine has been examined at intervals of six months for several years and it has always been reported negative as to albumin.

Present Illness.—Last summer he began to go down. He seemed anemic and inert and displayed a lack of interest in things in general. Last spring, he had an attack of shortness of breath accompanied by wheezing in the chest. He has had pain in his abdomen more or less for 10 or 15 years. He thinks he has passed more urine than normal for several years. About two weeks prior to this date he had severe pain in the abdomen. This has gradually grown worse. It was for this symptom that he consulted a physician. Other symptoms with the exception of constipation are not noted.

Physical Examination.—The patient is an undernourished man, of pale appearance, and looks more than 50 years of age. Temperature 98° F. (36.66° C.), pulse 100 per minute, blood-pressure 220-160. Heart is hypertrophied. The eyes react to light and accommodation. The teeth are bad. The throat is red; the patient complains of soreness where the tonsils were removed several years ago. The neck is negative. *Abdomen:* There is pain on pressure in the region of the umbilicus; neither the liver nor spleen is palpable; the skin, bones and joints are negative, except for the pallor noted above.

Laboratory Findings.—*Urine:* Voided specimen, amber, clear, albumin, +; sugar, negative; casts, hyalin and finely granular + + +; red blood-cells +; pus cells +. *Blood:* Hgb. 72 per cent. (Sahli); red cells 4,330,000; white cells 12,400; polymorphonuclears 76 per cent.; small lymphocytes 14 per cent.; large mononuclears 8 per cent.; transitional 2 per cent. Wassermann negative.

Special Examinations.—X-ray showed stomach filled well, and somewhat hypertonic in type. Fairly good duodenal cap was obtained under fluoroscope. It emptied in about 5 hours. Small intestines showed spastic and dilated areas scattered along the entire tract. The appendix was very much dilated and did not fill well. The cecum and ascending colon retained barium for 3 days without any passing the hepatic flexure. Barium enema filled the entire colon, and this area showed no obstruction, but a very large colon with very little activity. Barium was adhering all along the course of the intestinal tract, indicating low grade colitis. The teeth showed marked pyorrhea with a small abscess of upper right central. The pain in the abdomen subsided under large doses of benzyl benzoate. He had no fever at any time.

MODIFIED MOSENTHAL (JULY 17, 1921)

Time	Quantity	Specific Gravity
10 A. M.	120 c.c.	1917
12 M.	240 c.c.	1015
4 P. M.	80 c.c.	1012
8 P. M.	180 c.c.	1015
Total day	620 c.c.
Total night	760 c.c.	1013
Total 24 hrs.	1340 c.c.
Total fluid intake	2500 c.c.

July 19, 1921, blood urea, 40.5 mg. per 100 c.c. Patient had been on a very low protein diet for several weeks. July 26, 1921, blood hemoglobin 65 per cent.; red cells, 3,300,000; white cells 17,600; polymorphonuclears 82 per cent.; small lymphocyte 11 per cent.; large mononuclears 7 per cent. Blood urea, 63.5 mg. per 100 c.c. Urine: August 16, 1920, clear, yellow, specific gravity 1012, acid, albumin and sugar negative, microscopically, hyalin casts, cylindroids, pus cells + +, epithelial cells +, red blood-cells + +. Blood urea 122.5 mg. per 100 c.c. The eye-grounds showed albuminuric retinitis. Signs of complete cardiac decompensation developed in the last 10 days or two weeks of his illness. The patient died of uremia.

Clinical Diagnosis.—Malignant hypertension, combination form (nephrosclerosis), angina abdominalis, myocardial insufficiency, and uremia.

ILLUSTRATIVE CASE NO. II.—Mr. J. V. R., male, age 62, married, lumber business, March 4, 1921.

Chief Complaint.—Aching of legs on walking; fullness in chest on exercise. Duration 5 or 6 years.

Family History.—Father died of paralysis; mother, at 60, of kidney trouble; 5 sibs; one died of angina pectoris; one of paralysis.

Past History.—Had the ordinary diseases of childhood, a slight attack of dilatation of the heart 5 years ago. Has had erysipelas twice in the last two years.

Present Illness.—Feels pains in his legs on exercise and some fullness in the chest on exercise, no pain, no palpitation, no swelling of the feet. He has a slight cough, a good appetite, no indigestion, no colic and the bowels move regularly. No symptoms referable to the urinary system.

Physical Examination.—The patient is fairly well nourished. Temperature 98° F. (36.66° C.); pulse 78 per minute; blood-pressure 170–100. The head and neck are negative. The heart is hypertrophied. Apex in the sixth interspace, outside the midclavicular line. All of the palpable arteries are sclerotic. The abdomen and nervous system are without abnormal findings.

MOSENTHAL TEST

Time	Quantity	Specific Gravity
10 A. M.	172 c.c.	1012
12 M.	190 c.c.	1010
2 P. M.	130 c.c.	1010
4 P. M.	100 c.c.	1012
6 P. M.	190 c.c.	1010
8 P. M.	190 c.c.	1010
Total day	962 c.c.
Night urine	970 c.c.	1012
Total 24 hrs.	1932 c.c.
Total fluid intake	2000 c.c.

Albumin a trace, hyalin and granular casts. Phenolsulphonephthalein output, 20 per cent. in the 2 hours and 10 minutes. Blood urea, 80 mg. per 100 c.c. About six months after this examination the patient died suddenly from an attack of angina pectoris.

Clinical Diagnosis.—Malignant hypertension, combination form (nephrosclerosis), and angina pectoris.

ILLUSTRATIVE CASE NO. III.—Mr. C. L. C., male, 61, married, planter. Consulted author at his office, May 17, 1921.

Chief Complaint.—General weakness, tires very easily. Burning of feet, some dizziness, headache. Patient complains chiefly of high blood-pressure.

Family History.—Father died of blackwater fever; mother is dead, cause unknown. One brother died from high blood-pressure with paralysis; 4 sisters died of blackwater fever. One brother died of liver trouble and one of pneumonia.

Past History.—Has had measles, pertussis, typhoid fever, blackwater fever. His general health has been good until seven years ago. About four years ago he had some ear trouble—indefinite.

Present Illness.—For about seven years the patient has had attacks of dizziness; he walks with difficulty, especially in the dark. He has been gradually getting weaker—tires very easily. He has lost some weight, but does not know how much. He has marked shortness of breath and palpitation of the heart on exercise. He has not noticed any swelling of the feet or legs. He occasionally has pain below the right costal border, gets a little yellow and has "bilious attacks" at times. The pains have no reference to eating. He is very constipated. He thinks his urine is scant and he has to get up several times at night to void. He has a cramping sensation in the right arm and hand and some ringing in the ears.

Physical Examination.—The patient is very much undernourished and presents a pale appearance. Temperature 98° F. (36.66° C.); pulse is 72 per minute and regular. Blood-pressure is 260–110. There is visible pulsation in the vessels of the neck. The aorta is palpable in

the suprasternal notch and the supracardiac area of dulness is widened. The apex is in the seventh intercostal space, $1\frac{1}{2}$ ins. (3.81 cm.) outside the midclavicular line. At the apex, there is a systolic thrill and murmur; the latter is heard in the back. There is a systolic thrill over the aortic area at the base and the aortic second is markedly accentuated. The lungs are negative. The liver is palpable below the costal margin, the spleen is not palpable. The pupils and reflexes are normal. *Urine (Voided Specimen)*: Pale, yellow, acid, specific gravity 1010, albumin a trace, sugar negative, microscopically, casts +, epithelial cells +, a rare pus cell. *Blood (Stained Specimen)*: Anisocytosis, polychromatophilia, polymorphonuclears 70 per cent., small lymphocytes 24 per cent., large mononuclears 6 per cent., Wassermann 3 +.

Kidney Function.—Phenolsulphonaphthalein, 5 per cent. in 2 hours and 10 minutes. Blood urea, 85 mg. per 100 c.c.

Clinical Diagnosis.—Malignant hypertension, combination form (nephrosclerosis), and relative myocardial insufficiency.

ILLUSTRATIVE CASE NO. IV.—Mr. A. P. L., age 54, married, merchant-farmer. Consulted author at his office, August 17, 1921.

Chief Complaint.—Partial paralysis right side of body, following stroke two years ago. Indistinctness of speech. Shortness of breath and palpitation.

Family History.—Father died of Bright's disease; mother died of childbirth; one sib died of pneumonia, one of heart disease, one of pneumonia, and one of typhoid fever.

Past History.—Measles, mumps, pertussis, typhoid fever, has had a few attacks of bilious colic accompanied by jaundice, and a stroke of paralysis two years ago.

Present Illness.—About two years ago he had an attack of paralysis of the right side of the body. This came on gradually without loss of consciousness. This is much better now, but he still has some difficulty in using the right arm and leg and his speech is indistinct. He has marked shortness of breath and palpitation on exercise, but no swelling of his feet. He has nausea and a heavy feeling in the epigastrium two or three hours after eating. He rarely vomits, is constipated, and his appetite is poor. He has been losing weight rapidly lately, about 40 pounds in the last few months. Symptoms referable to the urinary system are negative.

Physical Examination.—The patient is fairly well nourished, though losing weight. Temperature 98.4° F. (36.77° C.); pulse 108; blood-pressure 240–150. The few teeth he has left are in fair condition. The left tonsil is very ragged and infected. Marked atrophy of the muscles of the right chest. *Heart*: The apex beat is heaving in the sixth intercostal space, one inch (2.54 cm.) outside the midclavicular line; the heart sounds are clear and there is marked accentuation of the aortic second. The palpable vessels are sclerotic. The abdomen is negative. The pupils are equal and react to light; the mouth is drawn somewhat

to the left; the tongue deviates a little to the left on protrusion. Se impairment of strength in grip of right hand. Knee-jerks are exaggerated on both sides, but markedly so on the right as are also arm jerks. Babinski slightly positive on both sides. Eye-grounds—arteriosclerotic hemorrhage and albuminuric retinitis.

Laboratory Findings.—Urine (voided specimen), cloudy, yellow, specific gravity 1012, acid, albumin +, sugar negative, microscopic field red blood-cells ++, epithelial cells +, motile bacilli +, casts +. Blood (stained specimen): anisocytosis; differential count, polymorphonuclears 79 per cent., small lymphocytes 15 per cent., large mononuclears 6 per cent. Wassermann, negative.

Functional Tests.—Phenolsulphonethalein, 6 per cent. in 2 hours and 10 minutes. Blood urea, 61.5 mg. per 100 c.c.

Clinical Diagnosis.—Malignant hypertension, combination form (nephrosclerosis), old hemiplegia, and relative myocardial insufficiency.

BIBLIOGRAPHY

Congenital Nephropathies

- ANDERS, J. M. Congenital single kidney, with the report of a case; the practical significance of the condition, with statistics. *Jour. Amer. Med. Assoc.*, March, 1910, cxxxix, 1.
- BRAASCH, W. F. The clinical significance of congenital anomaly in kidney and ureter. *Ann. Surg.*, 1912, lvi, 726.
- COPLIN, W. M. L. Unilateral renal hypoplasia and dysplasia due to defective arteriogenesis; relation to so-called hypogenetic nephritis. *Jour. Am. Med. Sc.*, March, 1917, cliii, No. 3, p. 381.
- EISENDRATH, D. N. Clinical importance of congenital anomalies of the kidney. *Surgical Clinics*, Chicago, October, 1917, 1, 1053.
- GERAGHTY, J. F., and PLAGGMEYER, H. G. The practical importance of infantile kidneys in renal diagnosis. *Jour. Amer. Med. Assoc.*, 1913, lxi, 2224-2226.
- GIBBON, J. W. Anomalies of the kidney and ureters and their embryological significance. *Jeffersonian*, Phila., 1916, xvii, 1-9.
- KEIBEL AND MALL. Human embryology. Vol. II. J. B. Lippincott Co., Philadelphia and London, 1912.
- KELLY AND BURNAM. Diseases of the kidneys, ureters, and bladder. Vol. I. D. Appleton & Co., New York City, 1914.
- MAYO, C. H. The surgery of the single and horseshoe kidney. *Ann. Surg.*, April, 1913, lvii, pp. 511-521, 6 pl.
- NEWMAN, D. Malformations of the kidney and its displacements without mobility with illustration of cases and specimens. *Transactions Clinical Society of London*, 1897-1898, xxxi, 118-157.
- Horseshoe kidney. *Lancet*, London, 1917, ii, 236.
- Pain in renal and vesical lesions. *Lancet*, London, 1916, i, 669-724.
- ROLLESTON, J. D. Single pelvic kidney. *Brit. Jour. Child. Dis.*, London, 1917, xiii, 80-86.
- STEIN, A. The clinical importance of unilateral fused kidney (including the dysplastic kidney of one side). *Amer. Jour. Obstet. and Dis. Wom. and Child.*, March, 1916, lxxiii, 449.

Blood										Complications and Associated Diseases
Red Cells	Leukocytes	Polymorpho- nuclears	Small Lymphocytes	Large Mononuclears	Eosinophils	Mast Cell	Wassermann	Eye-ground	Basal Metabolism	
		67	20	4			N	N		O
		76	21	3			N			O
3.8 Mil.	5.8 m.	71	23	6			N			O
							N			Been on diet for a year for alb.—sug. Diabetes
		71	16	9	3	1	N			?
		66	25	7		2	N			Beginning
		57	37	6			+++			Syphilis
3.75 Mil.	6 m.	71	28	1			N			O
		79	15	6			N			
		70	24	6			+++			Syphilis
		52	42	6			N			O
		81	15	4			N			Widened Aorta
4.1 Mil.		72	19	9			N			O
4.3 Mil. July 5		76	14	10			N			O
3.3 Mil. July 19		82	11	7						
							N			O
							++++			Syphilis
										O
										O
							++++			Syphilis
										O

indicates not present.

Movable Kidney

- BEHAN, R. J. Pain. D. Appleton & Co., New York, 1914.
- BRYAN, R. C. A few further remarks on the pathology and diagnosis of a dislocated or movable kidney. *International Clinics*, iii, 27th Series, p. 116.
- HARRIS, M. L. Movable kidney. *Transactions of American Surgical Association*, 1901, xix, 457.
- KELLY AND BURNAM. Diseases of kidney, ureter and bladder. Vol. I. D. Appleton & Co., New York City, 1914.
- MCALISTER, A. Nephroptosis. In Allbutt and Rolleston's *System of Medicine*, Vol. IV, Pt. I. The Macmillan Company, London, 1908.
- NEWMAN, D. Pain in renal and vesical diseases. *Lancet*, London, 1916, i, 773.
- PIERSOL, G. A. Human anatomy. Vol. II. J. B. Lippincott Co., Phila., 1918.
- BARKER, L. F. Monographic Medicine. Vol. III. D. Appleton & Co., New York City, 1916.

Uremia

- ASCOLI, G. Vorlesungen über Uraemie. G. Fischer, Jena, 1903.
- BRADFORD, J. R. General pathology of renal disease. *System of Medicine*, Allbutt and Rolleston. Vol. IV, Part I. The Macmillan Company, London, 1908.
- CHACE, A. F. Diet in interstitial nephritis. *Med. Clinics N. America*, Nov., 1917, i, 611.
- FOSTER, N. B. Uremia. III. The non-protein nitrogen of the blood. *Arch. Int. Med.*, Chicago, 1915, xv, 356-368.
- FOSTER, N. B., and DAVIS, H. B. The effect of water intake on nitrogen retention in nephritis. *Amer. Jour. Med. Sc.*, Phila., 1916, cli, 49-63.
- HERRINGHAM, W. P. Treatment of uremia: kidney diseases. Oxford Medical Publications, London, 1912.
- HOWLAND, J., and MARRIOTT, W. McK. Observations on acid-base equilibrium in the body. *Amer. Jour. Physiol.*, Boston, 1916-1917, xlii, 587.
- OSLER, Sir WM. Transient attacks of aphasia and paralysis in states of high blood-pressure and arteriosclerosis. *Canadian Med. Assoc. Jour.*, 1911, i, 919.
- PAL, J. Gefässkrisen. S. Hirzel, Leipzig, 1905.
- VAQUEZ, H. La tension arterielle dans le saturnisme aigu et chronique. *Semaine méd.*, Par., 1904, xxiv, 385.
- VOLHARD, F., and FAHR, T. H. Die Brightsche Nierenkrankheit. Julius Springer, Berlin, 1914.

Circulatory Nephropathies

- ALLBUTT, Sir C. Diseases of the arteries, including angina pectoris. Vol. I. The Macmillan Company, London, 1915.
- BARKER, L. F. Circulatory insufficiency. *Monographic Medicine*. Vol. II. D. Appleton & Co., New York, 1916.
- GIBSON, A. G. Insufficiency and dilatation of the heart. *Modern Medicine*, Osler and McCrae. Vol. IV. Lea and Febiger, Philadelphia and New York, 1915.
- HEWLETT, A. W. Functional pathology of internal diseases. *Monographic Medicine*. Vol. I. D. Appleton & Co., New York and London, 1916.
- HÜRTER. Untersuchungen am arteriellen menschlichen Blute. *Deutsch. Arch. f. Klin. Med.*, 1912, cviii, 1.
- LEWIS, T., RYFFEL, J. H., WOLF, C. G. L., COTTON, T., AND BARCROFT, J. Observations relating to dyspnea in cardiac and renal patients. *Heart*, 1913, v, 45.
- MCCALLUM, W. G. Cardiac valvular disease and its consequences in a textbook of pathology. W. B. Saunders Company, Philadelphia, 1916.

- McKENZIE, Sir J. Chronic diseases of the heart. Oxford Medicine. Vol. II. Oxford University Press, London, 1920.
- MOSENTHAL, H. O. Renal functions as measured by the elimination of fluids, salt and nitrogen, and the specific gravity of the urine. Arch. Int. Med., Chicago, 1915, xvi, 733-774.
- ROWNTREE, L. G. The treatment of nephritis. Practical Treatment. Vol. IV (The newest treatment). W. B. Saunders Company, Philadelphia, 1917.
- SIEBECK, R. Die funktionelle Bedeutung der Atemmechanik und die Lungen-ventilation bei Kardialer Dyspnoe. Deutsch. Arch. f. Klin. Med., 1912, cvii, 252.

The Nephropathies Generally Included Under the Genetic Term Bright's Disease

- ADAMI, J. G. Inflammation. The Principles of Pathology. Vol. I (General pathology). Lea and Febiger, Philadelphia and New York, 1908.
- ALLBUTT, Sir C. Loc. cit. supra.
- ASCHOFF, L. Harnapparat. Pathologische Anatomie, Dritte Auflage, Bd. II, Gustav Fischer, Jena, 1913.
- COUNCILMAN, W. T. Acute interstitial nephritis. Jour. Exp. Med., N. Y., 1898, iii, 305-420.
- FAHR, T. H. Über chronische Nephritis und ihre Beziehung zur Arteriosklerose. Virch. Arch., 1909, Bd. 195, 228.
- GASKELL, J. F. On the changes in glomeruli and arteries in inflammatory and arteriosclerotic kidney disease. Jour. Path. and Bacter., Cambridge, July, 1911, xvi, 287-321.
- JANEWAY, T. C. A clinical study of hypertensive cardiovascular disease. Arch. Int. Med., 1913, xii, 755.
- JORES, L. Über die Arteriosklerose der kleinen Organarterien und ihre Beziehung zur Nephritis. Virch. Arch., 1904, Bd. 178.
- LOHLEIN, M. Über die entzündlichen Veränderungen der Glomeruli bei menschlichen Nieren und ihre Bedeutung für die Nephritis. S. Hirzel, Leipzig, 1906.
- Über hämorrhische Nierenaffectationen bei chronischer ulceröser Endocarditis (Embolische, nicht Eitrige Herdnephritis). Med. Klin., 1910, Nr. 10.
- LUBARSCH. Entzündung. In Aschoff's Allgemine pathologische Anatomie. Vol. II, 374, cit. supra.
- MÜLLER, F. Morbus Brightii. Deutsch. patholog. Gesellsch., Meran, 1905.
- REICHEL, H. Über Nephritis bei Scharlach. Zeitschr. f. Heilk., 1905, xxvi, Heft I, 72.
- RIBBERT, H. Über Nephritis und über Entzündung parenchymatöser Organe. Deutsche. Med. Wehnsehr., 1909, Nr. 46, p. 1996.
- VOLHARD AND FAHR. Loc. cit. supra.
- WEIGERT, C. Gesammelte Abhandl., Berlin.

Nephroses

- EPSTEIN, A. A. Edema in chronic nephritis. Amer. Jour. Med. Sc., Nov., 1917, cliv, 638.
- FOSTER, N. B. Loc. cit. supra.
- FISCHER, M. H. Edema. Wiley and Sons, New York, 1910.
- HEINEKE, A. Veränderungen der menschlichen Niere nach Sublimalvergiftung. Ziegl. Beitr., Bd. 45.
- HEWLETT, A. W. Loc. cit. supra.
- MCCALLUM, W. G. Loc. cit. supra.
- OPHÜLS, W. Nephritis; a new series of cases with a review of recent literature. Jour. Amer. Med. Assoc., Chicago, 1915, lxxv, 1719-1725.

- MUNK, F. Klinische Diagnostik der degenerativen Nierenkrankungen. Zeitschr. f. Klin. Med., Berl., 1913, lxxviii, 1, 1 pl.
 NEWBURG, L. H. Production of Bright's disease by feeding high protein diet. Arch. Int. Med., October, 1919, xxiv, 359.
 PEARCE, R. M. The production of edema; an experimental study of the relative etiology, etc. Arch. Int. Med., Chicago, 1909, iii, 422-437.
 VOLHARD UND FAHR. Loc. cit. supra.

The Glomerulonephritides

- BAEHR, G. Significance of embolic glomerular lesions of subacute streptococcus endocarditis. Arch. Int. Med., Feb., 1921, xxvii, 262.
 EPPINGER, H., and KLOSS, K. Die Nephritisfrage. Verlag von Moritz Perles, Wein, 1921.
 HERRICK, J. B. Nephritis. Modern Medicine. Osler & McCrae, 2nd Edition, Vol. III. Lea & Febiger, Philadelphia and New York, 1914.
 JANEWAY, T. C. Nephritic hypertension; clinical and experimental studies. Amer. Jour. Med. Sc., Phil. and New York, 1913, cxlv, 625, 656.
 ——— Management of patients with chronic renal disease. Bull. Med. and Chir. Fac. Univ. Maryland, Baltimore, 1916, viii, 103-122.
 HULSE, W. Volhard's theory of glomerulonephritis. Deutsche med. Wehnschr., Nov. 4, 1920, xlv, 1244.
 HEWLETT, A. W. Loc. cit. supra.
 LOHLEIN, M. Über Nephritis nach dem heutigen Stande der pathologisch-anatomischen Forschung. Ergebn. d. inn. Med. und Kinderh., Berlin, 1910, v, 411-458.
 MÜLLER, F. Loc. cit. supra.
 ORTH, A. Pathologische Anatomie, Bd. II.
 OPHÜLS, W. Loc. cit. supra.
 O'HARE, J. P. A nephritic diet sheet. Amer. Jour. Med. Sc., 1920, cliv, 883.
 SIEGL, W. Experimentelles zur Frage der Erkältungsnephritis. Verh. d. xxv Kongr. f. inn. Med., 1908.
 VON NOORDEN, C. Clinical treatises on the pathology and therapy of disorders of metabolism and nutrition. Part II. Nephritis. E. B. Treat and Co., New York, 1903.
 CHRISTIAN, H. S. Nephritis. In Oxford Medicine. Vol. III. Oxford University Press, London and New York, 1920.
 VOLHARD AND FAHR. Loc. cit. supra.

Scleroses

- BARKER, L. F. The causes and treatment of the conditions underlying high blood-pressure. Ohio State Med. Jour., October, 1920, xvi, 709.
 JORES, L. The commoner diseases, their causes and effects. Woglom-Lippincott, 1915.
 MEARA, F. S. Hyperpiesia of Clifford Allbutt (essential hypertension). Med. Clinics North America, No. 1, W. B. Saunders Co., Phila. and London, 1918-1919, ii, 1.
 VOLHARD UND FAHR. Loc. cit. supra.
 ALLBUTT, Sir T. C. Loc. cit. supra.
 JANEWAY, T. C. Loc. cit. supra.

CHAPTER II

DISEASES OF THE KIDNEY

By ANTON G. RYTINA, A.B., M.D., F.A.C.S.

- Pyelitis, p. 691:—Definition, p. 691; Classification, p. 692; Etiology, p. 692; Symptoms and course, p. 694; Diagnosis, p. 695; Treatment, p. 696; Pathology, p. 699.
- Pyonephrosis, p. 700:—Definition, p. 700; Etiology, p. 700; Symptomatology, p. 701; Diagnosis, p. 702; Treatment, p. 702; Prognosis, p. 703; Pathology, p. 703.
- Perinephritic abscess, p. 704:—Definition, p. 704; Etiology, p. 704; Symptomatology, p. 705; Diagnosis, p. 705; Treatment, p. 706; Prognosis, p. 706; Pathology, p. 706.
- Hydronephrosis, p. 707:—Definition, p. 707; Etiology, p. 707; Symptomatology, p. 708; Diagnosis, p. 709; Treatment, p. 710; Prognosis, p. 711; Pathology, p. 711.
- Kidney and ureteral stone, p. 712:—Definition, p. 712; Etiology, p. 712; Symptomatology, p. 715; Diagnosis, p. 716; Treatment, p. 718.
- Calculus anuria, p. 720:—Definition and onset, p. 720; Symptomatology, p. 720; Diagnosis, p. 721; Treatment, p. 721; Pathology, p. 722.
- Cysts of the kidney, p. 722:—Classification, p. 722:—Multiple small cysts, p. 722; Large serous cysts, p. 722; Polycystic degeneration, p. 723; Dermoid cysts, p. 725; Paraneuritic cysts, p. 725; Echinococcus cysts, p. 725; Tubercular cysts, p. 724.
- Renal tumors, p. 727:—Introductory, p. 727; Benign renal tumors, p. 727; Malignant renal tumors, p. 729; Bibliography, p. 735.

PYEELITIS

(*Pyelonephritis*)

Definition.—Pyelitis is an inflammation of the kidney pelvis due to microbial infection. When one considers the frequency with which the term pyelitis is used, one would hardly realize that cases of pure pyelitis never occur, because bacteriological and pathological studies have shown the impossibility of having a pyelitis without an associated nephritis, so that the proper term should not be pyelitis, but pyelonephritis. However, from a clinical standpoint, there are certain cases in which inflammation of the pelvis is the dominating factor rather than the infection in the kidney, which may be trivial. Cases of this type respond better to treatment and are often curable, whereas cases of pyelonephritis do not offer the same chances for radical cure under treatment to be outlined later. The term dates from the time of Rayer, and has become so fixed as the word to describe the clinical condition of the mild or nonsurgical forms of pyelonephritis that it does not seem wise to discontinue it. Strictly speaking, every grade of kidney infection represents different degrees of the same process.

Classification.—Kretschmer divides pyelitis into the following clinical groups: (1) Defloration pyelitis, or the type occurring in newly-married women; (2) pyelitis of infancy and childhood; (3) pyelitis of pregnancy; (4) pyelitis following surgical operations; and (5) cases of simple pyelitis. Symptomatically, it is divided into the acute, subacute, and chronic forms.

Etiology.—Pyelitis is practically always caused by bacterial invasion and multiplication. Traumatism, elimination of certain irritant drugs, such as cantharids, cubebs, urotropin, etc., the alteration of the urine in certain diseases (sugar in diabetes) may cause renal congestion but not septic inflammation. Normally, the kidney can eliminate without harm to itself any variety of organism, the latter being carried to it by the blood current from a focus such as a purulent prostate or urethra, the bladder, intestine or from some far distant focus, *e. g.*, infected tonsils. In order to set up infection in the kidney or kidney pelvis, various factors are usually present, *e. g.*, a lowering of its resistance as a result of some general cause, such as anemia, overwork, worry, malnutrition or intercurrent disease. Pyelitis may be found in the course of various infectious diseases. Most commonly found, however, in the production of a pyelitis is obstruction in the urinary tract, which not only lowers the resistance of the kidney pelvis, but affords a favorable culture medium for the growth of various microorganisms. Obstruction alone though, in the urethra, bladder, or ureter will not cause suppurative pyelitis, but only a predisposition to it. For example, an aseptic ligation of one ureter leads to compression atrophy of the kidney on the corresponding side, whereas septic ligation is followed by suppurative processes. From what has been said, therefore, it is obvious, that certain factors are generally present before a pyelitis is set up, *viz.*, lowered resistance, urinary obstruction and pyogenic microorganisms. The healthy mucous membrane of the urogenital tract ordinarily resists septic infection, but there are exceptions to this rule and at times pyelitis will be set up without any apparent or discoverable cause. The most frequent cause of pyelitis is infection by the bacillus coli communis. Next in importance are the staphylococcus aureus or albus, usually the former, and the streptococcus. Other organisms, such as bacillus of typhoid fever, bacillus proteus, gonococcus, pneumococcus, bacillus mucosis capsulatis, bacillus pyocyaneus, etc., are rather uncommon invaders. It is not uncommon to find one or more types of organisms associated in the condition, particularly in the advanced stages of the disease. Infections with the tubercle bacillus are quite common, but on account of the importance of the condition it is described separately.

METHODS OF INVASION.—The portals of entry are: (1) Hematogenous (descending); (2) urogenous (ascending); and (3) directly from without, as in wounds of the kidney. Regarding the first two methods of invasion, *viz.*, hematogenous and urogenous, there has been much discussion in the literature. For a long time, it was thought that in practically every case the infection was urogenous (ascending), the organisms traveling upwards from the lower genito-urinary tract either by way of the lumen of the ureter, or that they ascend from the bladder, prostate, etc.,

to the kidney pelvis through the lymphatics connecting these organs along the wall of the ureter (Eisendrath and Schultz). It is practically settled that ascending infection by way of the lumen of the ureter never occurs unless an almost complete obstruction exists, or unless we are dealing with the rare type of ureter mouth that permits regurgitation upwards of fluids from the bladder to the kidney pelvis. In a normal bladder, there is no reflux of urine from the bladder to the kidney. It was at one time thought that this was due to the oblique direction of the ureter in the bladder wall. However, it is easy to show that this same reflux does not occur following the operation of ureter transplantation. If ascending infection occurs, therefore, we must conclude that the paths along which the infection travels must be through the lymphatics of the wall of the ureter and of the renal pelvis. That this method of infection occurs is undoubted, but of recent years the importance of this method of invasion is considered greatly exaggerated and has given way to the hematogenous theory of invasion. According to this theory, in the vast majority of pyelitis cases, the infection is blood-borne. The chief advocates of this theory are Cabot and Crabtree. According to these authorities, colon bacilli circulate in the blood during the early hours of symptoms due to colon pyelonephritis and can be demonstrated by blood culture. In a limited number of these cases blood infection has been demonstrated to be primary, followed in order by albuminuria, bacilluria and pyuria. The portal of entry of bacillus into the blood stream is not always demonstrable. The intestine, a purulent urethra or prostate, or an inflamed bladder, are the commonest sources of bacilli. Even in cases where the infection may have taken place along the course of the lumen of the ureter, owing to an incompetent ureterovesical valve or from lymphatic extension, Cabot and Crabtree were able to recover the bacilli from the blood stream, causing them to seriously doubt the occurrence of renal infection without the intervention of the blood stream. A third but rare portal of entry in pyelitis is directly from without, as is wounds of the kidney.

PREDISPOSING CAUSES.—Age.—Pyelitis may occur at any period of life, although the largest number of cases that come under observation are seen in adults. Recent observations have shown that pyelitis in infants and children is rather common. Many cases of so-called cystitis in children are in reality cases of pyelitis, as it is rare to find pure cystitis in children without concomitant pyelitis. Pyelitis may occur at any age, from a short time after birth up to seventy-five years of age. The largest number of cases, however, occur between the ages of thirty-one and forty (25 per cent.). The next largest number of cases occur between the ages of twenty-one and thirty (about 20 per cent.). From this it will be seen that practically one-half of the cases occur between the ages of twenty and forty.

Sex.—At one time renal infections in women were supposed to be rare. In recent years, however, owing to the perfection of modern urological diagnostic methods the contrary has been proven. Indeed, if ones takes into consideration the number of cases of pyelitis which are seen in women, such as pyelitis occurring during and after pregnancy, pyelitis in

female babies and children, the association of renal infection with lesions of the female generative organs, and the onset of renal infection after extensive gynecological operations, one may safely say that renal infections occur more frequently in women than in men. According to Kretschmer's studies, 61 per cent. of pyelitis occurs in females and 39 per cent. in males. Pyelitis is most often bilateral (about 60 per cent. of the cases). In the remaining 40 per cent. of the cases, the pyelitis is unilateral—the right kidney being more often involved than the left kidney.

Symptoms and Course.—The disease may be acute, subacute, or chronic. All are usually preceded by disease in the kidneys or other organs, even though at times they are not discoverable.

ACUTE PYELITIS.—Acute pyelitis usually begins with chills, high fever, and sweats. The temperature may reach as high as 105° F. (40.6° C.). The type of fever in acute pyelitis is not characteristic. It may be continuous, intermittent, or remittent. The height of the temperature does not depend upon the severity of the case and bears no special relation to the amount of pyuria and bacilluria. The constitutional phenomena usually attendant upon any febrile affection are present. The tongue is dry, thirst is experienced, and there is hebetude. Nausea and vomiting either alone or combined, severe pallor and marked prostration may develop. The urine contains much pus, many bacteria, heavy albumin ring, and some red blood-cells. Casts are not present in pyelitis, nor do they occur in pyelonephritis as a rule. Their constant presence points toward pyelonephritis, but their absence does not exclude the possibility of the latter affection. As a rule pain referable to the kidney is not found. Occasionally, however, the renal region is sensitive and rarely a distinct renal colic may be complained of. If renal sensibility becomes marked, persists, and if the chills and fever recur, suspicion concerning the formation of a kidney abscess is in order, and the same should be watched for. The urinary symptoms do not exhibit anything characteristic and may be present in any number of affections of the urinary tract. The urinary symptoms are mostly due to an attendant bladder involvement and consist in frequency, burning of urination, painful urination, urgency, difficulty and incontinence of urine. These symptoms may also be present, even though there is no cystitis present. Death occurs, sometimes within a short period, from coma, often with typical uremic convulsions. In other cases, the fever subsides suddenly as if by crisis, or it may become remittent in character; in still others it gradually reaches normal and the patient recovers or passes into the chronic stage.

CHRONIC PYELITIS.—It is not uncommon for the acute type to lapse into the chronic form. More frequently, however, the latter form develops insidiously without being preceded by the acute process. It should be remembered that chronic pyelitis may exist over a number of years without a history of fever or urinary disturbance and be diagnosed accidentally on finding pus or bacteria in the urine. More commonly, however, the patients in addition to the physical findings in the urine have certain urinary symptoms referable to the bladder, *e. g.*, frequency, painful and burning urination, urgency, hesitancy, dribbling, or incontinence of urine. The latter symptoms frequently lead to the diagnosis of cystitis,

and very often the patients have been subjected to local treatment referable to the bladder over a long period of years without benefit. It is a good rule to subject every patient suffering with urinary symptoms and changes to a ureter catheterization, unless the vesicle origin of the affection is made practically certain by the finding of organic disease in or around the bladder, *e. g.*, prostatic hypertrophy, stricture, gonorrhea, and spinal cord disease. Even in these cases, a pyelitis may also be present. The physical findings of the urine are practically the same as described under acute pyelitis. The presence of red blood-cells may be absent. If the drainage of pus from the kidney is hampered by inspissated pus and the ureters partly or entirely obstructed, symptoms of acute pyelitis may be set up. Similarly, if the focus of infection is not located, exacerbation may occur and convert the chronic type of pyelitis into a temporary, acute form.

Diagnosis.—The diagnosis of pyelitis as a rule is not very difficult. Even before the diagnosis of pyelitis is made, it is necessary that the patient be subjected to a careful examination, not only of his urine, but the use of the cystoscope, ureter catheter, x-ray, functional test, wax tip bougie, and the pyelogram are necessary, in order to exclude the possibility of some organic lesion of the urinary tract being responsible for the pyelitis. Urine examination reveals urine that is cloudy, and shows a marked ring of albumin. Macroscopically the cloudiness is due to pus and bacteria. Usually a few red blood-cells and desquamated, epithelial cells are found in the urine. By means of the cystoscope and double ureter catheter examination, not only the condition of the bladder is ascertained, but the source of the pus, whether from the right side, left side, or both sides, is learned. Having determined this point, the next step is concerned with the differentiation of the various lesions which are associated with pyuria and pus in the urine. Lesions such as ureter stricture and stone, renal calculus, renal tuberculosis, tumor, hydronephrosis, must be eliminated. By means of the plain x-ray and the wax tip ureteral bougies, stone in the kidney and ureter must be eliminated. However, in rare instances, even the possibility of small stones in the kidney or ureter may be overlooked. Every case of pyelitis should be potentially considered as one of renal tuberculosis, masked by the presence of the colon bacillus. The elimination of a diagnosis of tuberculosis should be obtained not only by careful microscopic and bacteriological examinations of the urine, but repeated guinea pig inoculations should be carried out. The suspicion of kidney tuberculosis is increased by the presence of changes in the bladder, particularly near the ureteral orifice of the affected side, seen through the cystoscope. However, kidney tuberculosis, masked by colon bacillus in the urine with negative cystoscopic findings, may be obtained. Stricture of the ureter, large hydronephrosis, and renal tumor, could be differentiated by the pyelogram. Another important point in the diagnosis of pyelitis is the carrying out of separate or relative functional kidney tests. In pyelitis, the phenolsulphonephthalein output from each kidney is practically normal, both from the point of time of appearance and quantitative output, but in pyelonephritis, especially if it is quite marked and very far advanced, there is a

decided reduction in the quantitative phenolsulphonephthalein output. Their differentiation has not only a decided value in differentiating pyelitis from pyelonephritis, clinically speaking, but has a definite prognostic significance in enabling us to predict whether or not treatment is going to prove curative. Because, in the cases of almost pure pyelitis, radical cure is often obtained, but only rarely so in the pyelonephritic types.

Treatment.—In cases of acute colon bacillus pyelitis, instrumental or local treatment is ordinarily contraindicated. Treatment should consist of rest, and careful regimen of the diet, forced water by mouth, and hexamethylenamin by mouth in doses of from 7.5 to 10 grains (.4924 to .65 gram) every four hours. Proper attention should be given to the gastro-intestinal tract, and particularly the avoidance of constipation and the use of free catharsis. There may be exceptions to the rule of not using local or instrumental treatment in acute pyelitis. For example, the author has succeeded in relieving the streptococcus septicemia of pregnancy accompanied by high fever and marked prostration by pelvic lavage, with the result of not only relieving the patient of her severe symptoms, but allowing her to go to the termination of a normal pregnancy. The cases of pyelitis of pregnancy seem to have more marked constitutional symptoms than the ordinary cases. Very often acute pyelitis will not respond to this method of treatment, and the case will lapse into the chronic type.

The treatment of subacute or chronic cases of pyelitis may be considered under the following heads: (1) Medical treatment; (2) vaccine therapy; and (3) pelvic lavage.

MEDICAL TREATMENT.—The treatment of pyelitis by drugs has but a small place. Various drugs have been recommended, such as the administration of bicarbonate of soda, $\frac{1}{2}$ to 1 teaspoonful, well diluted, three times a day. Salol has been highly recommended by some, but it has very little practical value. The only drug which is used by practically everyone is hexamethylenamin 7.5 to 10 grains (.4924 to .65 gram), well diluted in water every four hours. Its value is doubtful, as Hinman has shown that urotropin has little action at the level of the kidney pelvis. The acidity of the urine should be tested by examination with litmus paper, and if there is definite alkalinity, about 10 grains (.65 gram) of acid sodium phosphate should be given every four hours until the urine becomes acid, for the well-known reason that hexamethylenamin has no sure therapeutic value unless it acts in an acid medium. If for example, in some cases, urotropin causes vesical irritation or the production of hematuria and is contraindicated, benzoic acid should be substituted. From a medical or internal standpoint, however, more important than the drug administration is the drinking of large quantities of water. Lithiated spring waters or other proprietary waters have no greater value than ordinary drinking water, unless it be given for its psychological effect.

VACCINE THERAPY.—Vaccine therapy has been given a thorough trial in the treatment of pyelitis, but has given the same futile results in this disease that it has given in most diseases wherein it has been tried. However, there are a number of authorities who believe in their efficacy and

highly recommend them. A certain percentage of cases of pyelitis get well without any treatment whatever, and it is quite probable that cases of pyelitis which respond to vaccine therapy really belong to this class.

PELVIC LAVAGE.—Of all the various forms of treatment that have been used from time to time in the treatment of pyelitis, the latest form of treatment and one which has stood the test of time and which is undoubtedly the most effective, is that of **pelvic lavage**. This method of treatment consists in the **catheterization of the ureters** on one or both sides, depending upon whether the infection is unilateral or bilateral; then there is made a test of the capacity of the kidney pelvis by the introduction of sterile water through the syringe, followed by the introduction of a smaller amount of some medicated solution, usually from 8 to 10 c.c. injected through the catheter into the kidney pelvis. A large number of different drugs have been used for this purpose, for example, aluminum acetate, the organic silver salt preparations, such as colargol, argyrol, cargentos, silvol, etc. There is one drug, however, which has a more or less specific action on pyelitis when introduced into the kidney pelvis through the ureter catheter, namely, **silver nitrate**. The strength of the silver nitrate is from 1 to 2 per cent.; in most instances a 1 per cent. solution will suffice. Geraghty uses silver nitrate solution up to as high as 5 per cent. for the treatment of pyelitis. More recently 1 per cent. **mercurochrome solutions** have been used successfully in the treatment of pyelitis. The advantage of the latter solution is that it is more penetrating and less irritating than the silver nitrate solution, and at least equally as effective and perhaps more effective as a bactericidal agent. The two drugs should be used interchangeably, being substituted the one for the other if the desired result is not obtained as rapidly as one would expect. If the precaution is taken to measure the pelvic capacity before the introduction of the solution, pain and kidney colic will be most often avoided. The treatment is carried out as far as possible about every four or seven days, and continued not only until the urine is clear and free from pus and microorganisms microscopically, but until sterile cultures are obtained. Negative urinary findings, both microscopically and culturally, must be repeated a number of times before the case can be discharged as cured.

TREATMENT OF CHILDREN.—Some little modification of this plan of treatment should be followed in the treating of pyelitis in children. The strength of the silver nitrate or mercurochrome solution should be about one-half the strength used for adults, and the amounts used should vary from 1 to 4 c. c., depending upon the size and age of the child. Until recently the possibility of treating children by **cystoscopic methods** was not sufficiently appreciated. This has been due to the fact that the family physician and pediatrician consider instrumentation in small children impracticable on account of the caliber of the urethra. We now have available cystoscopes, which will allow easy treatment in female children, with the exception of very young babies. In young boys, however, a perineal section would first be necessary. Such instrumental treatment may be justifiable, if the patients are the subjects of a persistent infection that is sapping their vitality and causing invalidism.

INDIRECT METHOD OF TREATMENT.—The above outlined treatment may be considered under the head of direct method of treatment, but sometimes more important and necessary than the direct method of treatment is the indirect or accessory method of treatment. A careful history and physical examination should be made of the patient's entire body. X-rays of the teeth should be made, and infected tonsils removed. A careful examination of the gastro-intestinal tract is most important. The relationship between chronic constipation and other bowel conditions in the production of pyelitis has already been pointed out. The author has seen patients cured of recurrent attacks of pyelitis by the simple method of preventing chronic constipation. Various rectal conditions are undoubtedly important exciting factors in causing or keeping up colon bacillus pyelitis. These rectal conditions, such as fistulæ, fissures, hemorrhoids, should receive adequate treatment. A very common cause for the persistence of pyelitis, even after the most direct treatment, both local and internal, is the failure to recognize the important connection between infection in the prostate and seminal vesicles and pyelitis. If this fact is recognized, and the infection in the prostate and seminal vesicles is relieved by regular and systematic massage of both these organs and by irrigations, not only is the cure by the direct method hastened and achieved, but very often relapses and reinfections are prevented. Similarly, attention should be given to certain lesions in the pelvic organs of females, which are undoubtedly provocative of pyelitis. **Antiseptic douches** should be recommended, and various surgical procedures carried out, if pathological conditions in the female generative organs are accounted for, such as cystocele, rectocele, fibroid of the uterus, etc.

TREATMENT DURING PREGNANCY.—There is a more important group of cases to be considered from the standpoint of treatment, namely, pyelitis that occurs during pregnancy or the puerperium. Three methods of treatment have been advised for this condition of pregnancy, namely: (a) Emptying of the uterus; (b) surgical removal of kidney; and (c) pelvic lavage. The first two methods are too radical, and should be rarely if ever considered. The author has treated a number of cases of pyelitis of pregnancy in which the patients were highly toxic, and where interferences, such as the termination of pregnancy, or surgical interference upon the kidney, seemed necessary, yet he succeeded by **pelvic lavage** in not only relieving the patients of their symptoms but in permitting pregnancy to extend to the normal period. If conscientious and prolonged treatment of the pyelitis of pregnancy by pelvic lavage and other methods of treatment fail, and the patient is getting progressively worse, then consideration of the above-named surgical interventions may be in order.

SELECTION OF CASES FOR TREATMENT.—It is obvious that before resorting to treatment for pyelitis in the above-named manner, organic disease of the urinary tract must be eliminated by careful urological study. It will be impossible to cure cases of pyelitis by lavage, etc., if there exists as the provocative factor organic lesions of the urinary tract which call for surgical treatment. It is also well to remember

that certain cases of colon bacillus infection leading to the diagnosis of pyelitis may mask the presence of renal tuberculosis, and that every case of pyelitis should not only have a careful, microscopic study for the tubercle bacillus made, but inoculation experiments in the guinea pig are also necessary. The author recently had a case in which the patient had marked pyuria, with the colon bacillus present from the right kidney, and in which the negative results were obtained after careful, microscopical study to demonstrate the tubercle bacillus. The patient had more than a normal function in this kidney, but inoculation experiments proved the condition to be tuberculosis. More important than the above was the knowledge obtained after further study, of the complete absence of the opposite kidney. In concluding consideration of the treatment of pyelitis, one must recognize that any form of treatment will at some time fail to achieve a cure. If the patient is suffering with an advanced form of pyelonephritis, internal treatment or vaccine therapy will fail. Pelvic lavage will also fail, because the infection is so generally disseminated not only through the pelvis, but the medulla and cortex of the kidney, that the silver nitrate solutions do not come into contact with the infective foci. However, the cure of chronic pyelitis can be obtained in about 60 or 70 per cent. of cases by the methods of treatment outlined. In certain cases of pyelitis or pyelonephritis of this advanced type, even though the patients cannot be finally discharged with urine sterile and free from pus, their well-being can be markedly improved and their lives prolonged.

Pathology.—The changes exhibited by the pelvis of the kidney, the seat of infection, may be designated as catarrhal, suppurative, hemorrhagic, membranous, and gangrenous. In the catarrhal variety, the mucous membrane becomes congested and is covered with a thin layer of pus or mucopus. If the inflammation becomes more extensive and ecchymotic areas develop, the term hemorrhagic is applicable. In the suppurative variety, the pelvis contains free pus, there is an inflammatory thickening of the pelvic walls, the pelvis becomes distorted, and ulceration occurs on its surface. Some pouching of the pelvis may occur sufficient to allow an accumulation of pus like the "bas fond" of the bladder seen in prostatic hypertrophy. This pus accumulation, plus the swelling of the mucous membrane, may cause sufficient encroachment upon the caliber of the ureteropelvic juncture to close it.

The membranous type is that form of pyelitis in which the pelvis is covered by a membrane made up of shreds of fibrin and bacteria, giving the surface the appearance of a diphtheritic membrane. Areas of ulceration or gangrene may be noted, either localized or general. There is also some change to be noted in the ureter as a rule, although in some cases it may show no changes whatever. The ureter change may vary in its degree of involvement. It may be dilated or hypertrophied. Indeed, all the changes described as occurring in the pelvis may be noted in the ureter. The practical significance of this is that in treating pyelitis by pelvic lavage, the catheter should not be introduced too far up into the ureter before making injection in order to secure medication of the ureter itself. In cases where the condition

is more of a pyelonephritis than a pyelitis, in addition to changes noted in the pelvis, there are changes to be noted in the kidney. The kidney becomes small and dense, and shows a lobulated surface with an adherent capsule, and perhaps a small number of cysts containing serum or seropurulent substance. The chief changes are noted in the cortex. The latter may show fibrous tissue degeneration, containing lobules of fat. There may be nothing abnormal in the pyramids. Histological section reveals an infiltration of the stroma, with fibrous and fatty tissue which by their contraction cause obliteration of both tubules and glomeruli. This interstitial fibrosis is irregularly distributed, and where sclerosis is not present, the secretory epithelium tends to undergo compensatory hypertrophy.

PYONEPHROSIS

Definition.—Pyonephrosis may be defined as an accumulation of pus in the kidney pelvis or parenchyma. It ordinarily is impossible to draw sharp lines of distinction between the various forms of kidney infection. The distinction is arbitrarily made and for the convenience of description. For example, we often have the sequence of pyelitis, then pyelonephritis, and subsequently pyonephrosis. In the type of cases described as pyonephrosis, there is always associated a pyelonephritis, unless the pathological process has extended to such an extent that there is an entire destruction of the kidney parenchyma by the suppurative process, until the kidney is represented by a mere pus sac.

Etiology.—The same factors as well as the same organisms operative in the causation of pyelitis or pyelonephritis are active also in the production of the more serious kidney lesions. In addition to the above, there is always present in pyonephrosis some form of obstruction to the urinary outflow. The obstructive lesion may be anywhere between the kidney pelvis and the urinary meatus. Its most common location is at the ureteropelvic juncture. If the obstruction leading to back pressure changes in the kidney pelvis or parenchyma are unattended by microbial infection, the condition of hydronephrosis develops (*q. v.*). Pyonephrosis may be then defined as an infected hydronephrosis. This is true, but it may also develop in a kidney secondary to a pyelitis or pyelonephritis in which there was not at any time present a hydronephrotic kidney. The former type of pyonephrosis is termed a primary pyonephrosis. The methods of invasion described under pyelitis apply to pyonephrosis. It is difficult to state just when a pyelonephritis is converted into a pyonephrosis. According to Kelly and Burnham, any pelvis which contains 30 c.c. or more of pus should certainly be classified as a pyonephrosis. The amount of pus which may be present in pyonephrosis varies from 30 c.c. to inordinate amounts, even up to as much as three quarts. These enormous pyonephrotic cases are seen mostly in the type of cases which primarily were hydronephrotic. In pyonephrosis secondary to a pyelitis or pyelonephritis, there is often noted a marked destruction of the kidney parenchyma, but only moderate dilatation of the kidney pelvis.

Symptomatology.—The clinical picture of pyonephrosis is most variable and the symptomatology may vary from the one extreme of having an enormous pyonephrotic sac filled with purulent material without symptoms, to the other extreme of a relatively small pyonephrosis producing the most profound symptoms of sepsis. The variability of the symptomatology corresponds greatly to the heterogeneousness of the underlying pathological process. Pus in urine is about the only thing that is common to all open forms of pyonephrosis. It exists as long as there is communication between the kidney pelvis and bladder. It may cease temporarily or permanently—temporarily, if the obstruction occasioning it (*e. g.*, plug of inspissated pus, or stone at the ureteropelvic juncture) is removed, and permanently, if the obstruction persists, or if the kidney undergoes suppurative dissolution. The above characteristics have given rise to the terms open and closed pyonephroses. The asymptomatic type of pyonephrosis is most generally seen in the form of open pyonephrosis or where free drainage exists between the kidney pelvis and the urinary channel below. Should occlusion of the ureter take place, however, free drainage is interfered with, absorption of toxins follows, resulting in constitutional symptoms, such as fever, chills and sweats, weakness, anorexia, increased pulse rate, leukocytosis, etc. The latter symptoms, however, do not necessarily indicate a temporarily closed pyonephrosis. They may also be noted in open pyonephrosis, due to an active suppurative process and destruction going on within the kidney parenchyma. Again, closed pyonephrosis may occur without producing fever and its allied symptoms. The urine in a closed pyonephrosis clears up and remains cleared until the obstruction occasioning it is relieved, providing there is no permanent focus elsewhere in the urinary tract. However, a large percentage of cases of pyonephrosis have at least an associated pyelitis of the opposite kidney. The next most prominent symptom of pyonephrosis is pain or tenderness in the renal region. This symptom, too, is variable and the reason therefore easily understood, if we are familiar with the pathology and the mechanical force which may be at work in pyonephrosis. The pain may be spontaneous or elicited only on deep pressure. As often as not pain is entirely absent, even after deep pressure over the kidney region. Usually, however, a feeling of heaviness or a dragging sensation is felt in the back over the kidney region, and accentuated after deep pressure is made. Furthermore, the patient may have the most violent paroxysms of pain exactly simulating renal colic due to occlusion of the ureter and damming back of the urine and pus into the kidney pelvis or parenchyma. Palpation of the kidney with the idea of feeling the tumor mass is most unreliable. The kidney may not be much increased in size, or it may be hidden behind the confines of the thorax, or the patient may be too stout or muscular. However, if the distended renal sac lies below the arch of the thorax and is quite large, or can be brought below the arch of the ribs by inspiration, it can usually be readily palpated. Vesical symptoms due to a concomitant disease of the bladder, prostate or urethra, owing to descending infection may be most pronounced. These symptoms and their manner of production have

been sufficiently discussed under the heading of pyelitis (*q. v.*). Just as often, however, vesical symptoms will be entirely absent.

Diagnosis.—Ordinarily, the diagnosis of pyonephrosis is most easy, especially if the aids at the command of the modern urologist are made use of. If marked pyuria, pain on pressure and a tumor mass is felt in the renal region, the probability of pyonephrosis is great. However, by use of the cystoscope, ureter catheterization, renal functional tests, x-ray, and pyelography, the diagnosis is not only made certain, but much additional information is gained which aids both in enabling us to form the correct judgment concerning the proper treatment to be instituted, and in giving the right prognosis. By means of the cystoscope we learn the condition of the bladder interior, and what association direct or indirect in has in causing the symptoms. The ureter, catheter and renal functional tests, the phenolsulphonaphthalein test, chromocystoscopy, urine-urea elimination, etc., enable us to not only determine the source of the pus in the pyonephrotic kidney, but the amount of renal destruction already present. Moreover, it enables us to learn the condition of the opposite kidney: *i. e.*, first, whether the kidney is present or not; second, whether or not it is a congenitally atrophic or infantile kidney; and third and more important, it enables us to learn whether or not it is also infected and to what extent, and if it could carry on the necessary bodily renal function if radical treatment, such as nephrectomy, were contemplated. By means of the x-ray we can learn of the presence of stones and their location, and determine their amount of responsibility for the pyonephrotic condition. By means of the wax tip bougie in the ureter, we might detect a stone in the ureter causing obstructive symptoms leading to pyonephrosis. By means of pyelography, we can learn the amount of dilatation of the kidney pelvis and the amount of kidney destruction already present. From what has been said, therefore, it is obvious that a pyonephrosis patient should always have the services of a urologist, without whom intelligent treatment and diagnosis may be impossible. Indeed, it should be a cardinal rule never to treat a patient for pyuria until every means has been employed to determine its exact source and significance.

Treatment.—The treatment of pyonephrosis may be divided into the mechanical and operative. By the mechanical method of treatment we allude to means of combating or alleviating the condition without the aid of the knife. By the operative method, we mean resort to the knife.

MECHANICAL METHOD OF TREATMENT.—Pyonephrosis, being a condition due to obstruction and infection, is **never benefited by medicinal treatment of any kind.** The treatment must necessarily be mechanical in nature and consists in ureter catheterization of the infected side or sides and the carrying out of pelvic lavage as already described in pyelitis. The treatment by pelvic lavage is slightly different than that of pyelitis on account of the difference in the pathology present, *viz.*, pyelitis indicates septic inflammation of the pelvis, whereas pyonephrosis refers to septic inflammation, plus sac formation in the kidney. This factor requires, therefore, in addition to introducing antiseptic sub-

stances into the kidney, the washing out of the infected residual urine in the kidney by a process of irrigations or even permanent catheterization, the ureter catheter being left in the kidney for several hours or even as long as eight hours. It is surprising, at times, how much relief a patient can receive by this method of treatment. Proper drainage is instituted, septic absorption stopped, kidney function improved, and the patients are made more comfortable and life is prolonged. The mechanical treatment, however, is never curative and should be resorted to only when contraindications exist to the operative treatment.

CONTRAINDICATIONS TO OPERATIVE TREATMENT.—These consist of the following: (1) Cases in which the disease is advanced and bilateral; (2) cases in which the opposite kidney is absent or of the infantile type (congenitally atrophic kidney); (3) cases in which the disease is early and a large amount of secreting substance is present; and (4) cases complicating far-advanced pregnancy.

OPERATIVE METHOD OF TREATMENT.—The operative methods of treatment may be of three kinds: (1) **Nephrotomy**; (2) **nephrostomy**; and (3) **nephrectomy**. The selection of the proper form of operative intervention depends upon several factors, *e. g.*, the degree of illness of the patient. A very sick patient requiring radical operation whose vitality is low had better first undergo nephrotomy or kidney drainage under local anesthesia. Again, nephrotomy would be first indicated in a pyonephrotic kidney, if the condition of its mate has not been determined, or if its mate is also badly diseased. Nephrectomy, primarily, is always the operation of choice in pyonephrosis if the patient's physical condition warrants it, and if careful urological and laboratory examination reveals no contraindications. The advantage of this operation is that it is followed by rapid and permanent recovery, and the avoidance of troublesome renal fistula which may require subsequent secondary nephrectomy.

Prognosis.—The outcome of the disease is variable. It is surprising at times how patients who have marked pyonephrosis remain in good physical condition for months or even years. More often, unless interference is instituted, death occurs from uremic sepsis. Rupture into the ureter, into a neighboring organ and into the perinephritic fat may occur, giving rise to perinephritic abscess (*q. v.*). As already mentioned, the contents of a pyonephrotic sac may undergo a sort of caseation and become aseptic (Keyes).

Pathology.—The pathological changes present in a pyonephrotic kidney vary and are modified by the type of preëxisting lesion of which it is the culmination. The kidney may be nothing but a thin or thick wall-sac filled with purulent fluid. Puncture of the sac will cause the exit of the purulent fluid, which is usually thick and creamy, having a very foul odor, particularly if the *bacillus proteus* or certain strains of the colon group are responsible for the infection. The sac itself may show little or no vestige of former kidney tissue. Ordinarily, however, the interior of the sac is composed of a number of compartments, communicating or noncommunicating, separated by kidney tissue, some-

times fairly normal looking in appearance; more often, the kidney parenchyma shows evidences of interstitial fibrosis. The pelvis varies in the amount of its distention as already described. Its mucous membrane has lost its normal pinkish appearance entirely and is replaced by granulation tissue. The exterior of the kidney often presents a lobulated appearance, somewhat like an infantile kidney and in some cases it is not only adherent to the perinephritic tissue, but has caused certain inflammatory reactive changes in this region. The fatty capsule may be replaced by fibrous tissue, or it may be thickened and intimately adherent to the sac. Stones either of primary or secondary origin may be found. The size, shape and number may vary within wide limits. The ureter in pyonephrosis may present a fairly normal appearance, except in those cases where the pyonephrosis was secondary to obstructive changes in the lower ureter tract, or secondary to pyelonephritis when changes characteristic of the latter will be noted and which already have been described. Perinephritic abscess may be associated with pyonephrosis and is due to the rupture of the abscess into the perinephritic tissue, or the direct extension of the infectious organisms by contiguity of tissue. Pyonephroses are described as open or closed, this being dependent upon whether or not there is a patency or closure at the ureteropelvic juncture allowing or preventing communication between the kidney and the bladder. The condition may be unilateral or bilateral. If bilateral, a condition in which both ureter regions are equally obstructed is present, *e. g.*, prostatic hypertrophy, stricture of the posterior urethra or vesical neck, congenital valve formation, etc. Rarely, the second kidney may become pyonephrotic by hematogenous extension from its pathological mate primarily diseased. Occasionally adhesions to neighboring organs take place and rupture into them occurs. Exceptionally the contents of a pyonephrotic sac undergo a sort of caseation and become aseptic (Keyes).

PERINEPHRITIC ABSCESS

(*Perinephritis*)

Definition.—This condition consists of an inflammation of the fibrous (fatty) capsule surrounding the kidney. Suppuration does not always occur.

Etiology.—Inflammation may be primary or secondary. In the primary, the most common etiological factors are: (1) Trauma; (2) infectious disease; and (3) "colds" and hematogenous infections. The secondary follows infections of the kidney, as pyelitis, pyonephrosis, renal calculi, tuberculosis of the kidney, pyelonephrosis, or ureteritis. The primary focus may be at some distant point as the appendix, uterus, or its adenexa, spleen, gall-bladder or liver, tuberculosis of the spine or ribs, following removal of prostate or operations on other parts of the genito-urinary tract. Frank Kidd, of London, states, that from pathological findings many cases of perinephritis arise from a small

bacterial infarct situated just beneath the true capsule of the kidney, coming primarily from the blood stream and containing as a rule the staphylococcus aureus as the offending organism. It slowly burrows its way through the true into the fatty capsule, gradually digests this and is unnoticed until a large abscess is formed with its accompanying symptoms.

AGE.—It usually occurs in middle life, although extremes have been noted. It is generally on the right side and is most common in males. It may be bilateral or multiple when due to kidney disease.

Symptomatology.—The symptoms vary greatly depending upon onset, which may be acute or more commonly subacute. The location, as already stated, may be anterior, posterior, above or below the kidney. If the symptoms are acute and due to some kidney condition, you may obtain a history of this condition. The patient may have chills, temperature, prostration, and severe toxemia may be present. Urinalysis might be valuable. The blood-picture may show a septic condition unless due to tuberculosis. The abscesses, if situated, as is most common, behind the kidney, may first cause tenderness on palpation and later swelling in this region. If it progresses sufficiently, signs of pointing may appear, the skin taking on an edematous appearance, being reddened with a distinct mass formation. In this type, or in fact, the subacute as well, you find the patient favoring the affected side. If in bed, the thigh is adducted and flexed. If ambulatory, a limp is present. When the abscess follows any acute abdominal condition, as appendicitis, etc., the symptoms are masked by it. If the abscess has burrowed its way to the pleural cavity and formed a pneumopyothorax, the first symptoms which may appear are shortness of breath, cough, and dyspnea. Lung abscess may form, rupture and evacuate itself through the bronchus, causing a disappearance of most of the symptoms. Respiratory movements do not affect the abscess. It may also rupture into the kidney itself, ureter or bladder, confining symptoms to the genito-urinary tract; or into the colon and if so, pus in large quantities is found in the stools. Rupture into the peritoneal cavity may also happen, but this is rare. Tympany is present over the abdomen, but dullness is elicited over the lumbar region and does not change its position with that of patient. Pain varies in intensity and distribution according to the size of the abscess and its pressure on the surrounding nerves. It may radiate down to the genitalia or the thigh, or be confined to the lumbar region or abdomen.

TEMPERATURE.—The patient usually shows the septic type, but almost any type of chart may be obtained. Leukocytosis, unless the abscess is tubercular, is always present. Gastro-intestinal upset may be present in both the acute and the chronic case.

Diagnosis.—First obtain complete and thorough history, which may bring to light some previous infection either in the kidney itself, or in some other part of the body. Cystoscopy, urethral catheterization, repeated urinalyses, and functional tests and pyelography should be carried out when necessary. If the latter is not used, plain x-ray may

be of value. If a mass is present in the lumbar region, aspiration or exploratory operation may be necessary to clear the diagnosis. The following conditions often require elimination: Myalgia or lumbago, true renal colic, tuberculosis of the spine, ribs, or hips, appendicitis, and other inflammatory conditions in the pelvis. In some kidney conditions, as acute suppurative nephritis, pyelitis, neoplasms, and pyonephrosis, diagnosis is not made until operation is performed.

Treatment.—This is entirely in the surgeon's hands. Lumbar incision when possible with free drainage should be made. If kidney function is good, do not disturb; if poor with good function on opposite side, nephrectomy can be carried out by the use of a blunt dissection. The only medicinal treatment to be considered is that of an expectant or supportive nature.

Prognosis.—If the diagnosis is promptly made, and abscess points either in the iliac or the lumbar region, and thorough drainage is immediately carried out, the prognosis is very good. If rupture takes place into the pleura, it is grave. When rupture occurs into the kidney, ureters, bladder, or colon, the prognosis is influenced by the amount of damage done. If the abscess becomes encysted, complete recovery takes place.

Pathology.—Abscesses may be single or multiple. The fatty capsule is replaced by inflammatory tissue in the acute, and connective tissue in the chronic. The tissue varies very much in thickness. On cross section, it usually shows the presence of edema; what remains of the fatty capsule is infiltrated with connective tissues, and if the condition has been going on long enough the whole is replaced by cicatricial tissue. The position of the abscess may be in front, below or behind the kidney, the latter being the usual site. Depending upon its position, it finally dissects or burrows its way to the exterior, pleura, lungs, or bronchus, or evacuates itself into the intestines, kidney, bladder, or some other organ or part of the pelvis. The retrorenal abscess as a rule opens or makes its appearance at Petit's triangle. This of course, aids the surgeon as well as the patient, the former in his diagnosis and treatment, the latter as far the prognosis is concerned. Other points where this type may find its way are the iliac fossæ, thigh and groin, or it may travel upward into the pleural cavity. Abscesses which have their primary focus in the kidney may be multiple. As a rule the abscess is single and of large size before operated upon, containing as much as a liter (2.11 pints) of pus, which may be odorless. This, of course, depends upon the organism causing the condition. Occasionally at operation there is profuse hemorrhage. When the abscess is primary, or from some distant focus, the kidney itself may show an amyloid degeneration. Martin-Thomas-Moorhead claim that 4 per cent. of recorded cases reach the pelvis postperitoneally and open either into the rectum, vagina, urethra, or bladder. Also 6 cases on record ruptured into the colon, 4 of which recovered. In Fisher's 94 cases, 24 per cent. affected the pleura, 20 per cent. the lungs, and 6 per cent. the pericardium.

HYDRONEPHROSIS

(*Uronephrosis, Sackmiere (Kuster) Cystonephrosis, Nephrectasis, Renal Distention*)

Definition.—Hydronephrosis is a dilatation of the renal pelvis, calyces or parenchyma substance, one or all, caused by a damming backward of aseptic urine, due to an obstructive influence somewhere along the urinary tract.

Etiology.—Anything which prevents the urinary outflow from the kidney in a normal manner may result in the formation of a hydronephrosis. In reality, it is a symptom and not a malady, an effect and not a cause. The cause is always something obstructive in nature, and may lie within or without the urinary channel, at any point between the urinary meatus and the ureteropelvic juncture. To produce a hydronephrosis, however, the obstruction must have certain forms or characteristics, *e. g.*, complete, total, long-continued or permanent obstruction will not produce a hydronephrosis, but a renal atrophy. If the obstruction is complete, only if it is short-lived and oft-repeated will it cause the lesion: if the obstruction is partial it must be long-continued, oft-repeated or permanent in order to cause hydronephrosis. The nearer the obstruction is to the renal pelvis, the sooner will hydronephrotic conditions manifest themselves, *e. g.*, a stricture or calculus at the ureteropelvic juncture will produce the lesion much more quickly than a stricture or stone in the urethra. In order to appreciate the rationale of the above statements concerning hydronephrosis a few words concerning the renal pelvis will be helpful. The renal pelvis is a funnel-like dilatation of the upper end of the ureter, designed not to act as a urinary reservoir like the bladder, but to receive the urine from the various calyces and allow its easy passage into the bladder via the ureter. Under ordinary circumstances the urination is easy and unimpeded and even if a certain amount of obstruction from whatever cause should develop, hydronephrosis would not occur providing the amount of urine excreted did not exceed in amount that capable of trickling through the obstructive portion without causing a back-flow. When the amount of urine excreted by the kidney becomes greater than that which is allowed to flow beyond the obstructive region, dilatation, beginning first just behind the obstructive area, occurs and gradually extends upward to the kidney pelvis; then the calyces and finally the kidney substance will become involved in the process. Generally speaking the causes of hydronephrosis are congenital and acquired.

CONGENITAL HYDRONEPHROSIS.—Under this heading are grouped defects, mostly of the ureters, that are of congenital origin. Some of these ureteral anomalies that are responsible for the production of hydronephrotic lesions are the following: absence of the ureters, single or multiple ureters, abnormal position of the orifices, bends or twists, narrowing and valves of the ureters and imperforate ureters. There may also be included narrowing caused by the pressure exercised upon the renal pelvis or ureter by abnormally placed branches of the renal blood-

vessels. There is practically no congenital defect disturbing the bladder that gives rise to hydronephrosis; and in the urethra, the only congenital anomaly that may secondarily cause the formation of a hydronephrosis is the so-called congenital valve formation of the posterior urethra. Phimosis, and in rare instances, urethral stricture, may cause renal distention.

ACQUIRED HYDRONEPHROSIS.—The cause of acquired hydronephrosis may be found in any portion of the urinary tract, and the etiological factor may act from within or without.

URETERAL OBSTRUCTION.—The obstructions from within the ureter causing hydronephrosis are the following: stricture (most commonly at the ureteropelvic juncture), stone, tumor, or foreign body in the ureter. Pressure from without the ureter may rarely cause hydronephrosis, *e. g.*, pelvic growth, kinking or twisting of the ureter from abnormal renal mobility (nephroptosis), inflammatory adhesions, etc.

URETHRAL OBSTRUCTION.—This arises from enlarged prostate and stricture. These latter organic diseases accomplish their damage rather by infection than by distention. Inflammatory and ulcerative disease about the region of the urinary meatus may cause urethral obstruction.

THE FLUID.—The quantity of fluid in a hydronephrotic sac varies within wide limits. The normal pelvic capacity is about 7.5 c.c. with variation limits between 1 and 20 c.c. Hydronephrotic sacs have reached a capacity up to 5 or 6 gallons. Glass reported one case containing 30 gallons. The color and odor of the fluid is slight and of very low specific gravity. Urea, uric acid and other urinary solids may be greatly diminished or entirely absent. There is often found in the fluid some red blood-cells, desquamated epithelium, leukocytes, casts and albumin. There may be a slight associated catarrhal pyelonephritis which does not affect in any way the clinical aspects of the condition. A hydronephrotic kidney is prone to infection and when the latter occurs an infected hydronephrosis or pyonephrosis results.

Symptomatology.—The symptoms of hydronephrosis may be classified clinically into latent, intermittent, and persistent or fixed.

LATENT HYDRONEPHROSIS.—By latent is meant a hydronephrosis which exists without producing manifest symptoms or signs. It may be discovered postmortem, or during the routine of a complete urological examination.

INTERMITTENT HYDRONEPHROSIS.—In this type symptoms come irregularly and are characterized by severe attacks of pain in the side. The pain may exactly simulate renal colic. The intervals and frequency of the attacks vary. The pain after lasting several hours or days is suddenly relieved by the passage of a large quantity of urine. Oliguria is usually present during the stage of pain. During the attack the distended kidney may be felt completely filling the entire loin, although very severe attacks of intermittent hydronephrosis may be seen without evident tumor formation. After the attack, if a tumor has been present, it will be reduced in size or disappear entirely, to recur or become obvious at the next attack. Tenderness over the kidney region is often noted during the attacks. Prostration may be present but fever and

leukocytosis are absent. The usual sequence in intermittent hydronephrosis is its transition into the fixed or permanent type. The tumor mass tends to maintain its size and the pain becomes more constant but less aggravated. If the condition is bilateral symptoms of uremia may develop.

FIXED OR PERMANENT HYDRONEPHROSIS.—When the hydronephrosis is fixed or permanent, the patient may have remarkably few symptoms and enjoy a fair state of health. The patient usually gives a history of a slowly growing tumor in the region of the kidney, with a feeling of soreness or pain or a dragging sensation. The latter symptoms may be present before the tumor can be detected. The tumor grows very slowly. The urine passed is normal in amount and quality providing the condition is unilateral. In rare cases it may burst into the perinephritic space or the peritoneal cavity.

Diagnosis.—The one classical sign of hydronephrosis is a tumor in the loin. However, marked and well-formed bilateral hydronephrotic sacs may be present without evident tumor formations. From a therapeutic standpoint it is most important that the diagnosis be made before the development of a palpable tumor. With the employment of the modern urological aids at our command, in the vast majority of cases this ought to be easy; without them, extreme difficulty of diagnosis has often to be encountered. The conditions that may be confused with it are both renal and extrarenal. The extrarenal conditions that suggest hydronephrosis are the following: ovarian, pancreatic, mesentery cysts, encysted ascites, gall-bladder disease, appendicitis, and neoplasms of the liver and spleen. The renal condition that may simulate hydronephrosis, and with which it may be associated are: renal stone, neoplasm, tuberculosis, polycystic kidney, hydatid cysts, ureteral strangulation (Dietl's crisis), pyonephrosis, perinephritic abscess, etc. The differential diagnosis of these many conditions from hydronephrosis is usually easy to the urologist and it will be necessary to enlist his aid not only in determining more accurately the diagnosis but other factors as well, such as the grade or extent of the hydronephrosis, the functional capacity resident therein, the condition of unilaterality or bilaterality, the presence and condition of the other kidney, should nephrectomy be contemplated, etc. The location and nature of the obstruction and other data must be sought for. On this account, it does not seem necessary to go deeply into the differential diagnosis between hydronephrosis and the many other conditions enumerated above. A hydronephrosis that has developed to the stage of palpable tumor formation presents certain characteristics that make its diagnosis strongly presumptive, even before the use of the urologist's armamentarium. These characteristics are dullness on percussion and movements corresponding to those of the diaphragm. If the tumor is of moderately large size, the colon lies in front of it, and percussion may reveal a tympanitic rather than a dull note. If the hydronephrosis is of large size, the colon and intestines are usually displaced to the side. Sometimes in thin-bellied people the lobulated character may be made out and fluctuation may be recognized. Pain is a variable symptom, which fact is easily understood from the

study of the pathology of hydronephrosis, which has been sufficiently discussed under the heading of symptoms. The aids necessary in the diagnosis and intelligent treatment of hydronephrosis are: (1) The cystoscope; (2) ureter catheterization; (3) renal functional tests; (4) x-ray; (5) pyelography; and (6) wax tip.

THE CYSTOSCOPE.—If a tumor is felt in the loin, it may be possible to diagnose hydronephrosis by means of cystoscopy by observing the ureteral orifices, especially if the patient has previously received an injection of indigocarmin or methylene-blue. The absence of urinary flow on one side, with active flow on the other may be determined; more frequent contractions during polyuria, fewer during the stage of oliguria can be determined. Intermittency or continuousness of flow is recognizable. The indigocarmin elimination, both from the standpoint of its time of output and intensity of color, may give one an idea of the relative functional capability of the kidneys. In the early stage of hydronephrosis, the cystoscope will not prove very helpful and the ureter catheter must be employed. This aid should always be made use of on account of the great and necessary information it enables us to obtain. By it we can learn the character of the urine from each side, the functional ability of each kidney—especially the urea elimination output—and the pelvic capacity of each kidney. A pelvic capacity of 30 c.c. is considered sufficient to diagnose hydronephrosis and a pelvic capacity of 150 c.c. is regarded as indicative of much destruction of kidney tissue. By means of the ordinary x-ray we can not gather much information concerning the diagnosis of hydronephrosis, unless stone is the obstructive factor responsible for it. However, by using the x-ray in conjunction with the injection through the ureter catheter into the kidney pelvis of certain shadow-casting substance (sodium bromid, sodium iodid, thorium, collargol, argyrol, etc.), the diagnosis in the vast majority of cases can be clinched. By it the shape, size, and position of the kidney may be determined and often the distinctive cause responsible for the hydronephrosis may be seen. This is called pyelography or urography. Its application makes the diagnosis not only certain, but in the majority of cases it also renders easy its differentiation from the many organic conditions that might simulate it. Renal functional tests are not only great diagnostic aids, but prognostic as well. As has already been mentioned, one cannot judge of the functional capacity of a hydronephrotic kidney after pyelography or even at the time of an exploratory operation, but the greatest aid in this regard is obtained by the renal excretory tests properly employed, particularly, the phenolsulphonephthalein test and the urea elimination test. By these same tests the condition of the other kidney also is obtained which aids not only our judgment as to proper procedure of treatment, but also enables us to give the right kind of prognosis. By means of the wax tip, we can often learn of the presence of a stone in the ureter, when the ordinary x-ray fails to reveal its presence. We thereby learn to know it as the causative factor of the hydronephrosis.

Treatment.—In the treatment of hydronephrosis certain important considerations ought to be kept continually in mind, *viz.*:

(1) The condition ought to be recognized as early as possible or before much damage to the kidney has been done.

(2) The discovery and removal of the obstruction is the most important element in the treatment.

(3) Never remove a hydronephrotic kidney unless thorough study from all standpoints indicates this as the method of choice.

Medicinal treatment is valueless in the treatment of hydronephrosis. Some form of **surgical or mechanical treatment** has to be employed, either for the purpose of relieving the obstruction or, when this is impracticable or impossible, of relieving the condition itself. Aspiration, except in doubtful cases for diagnostic purpose and then rarely, is mentioned only to be condemned. The dilatation of the ureter by the ureter catheter may occasionally relieve the condition. The **operative measures** for relief of the cause of hydronephrosis and the condition itself follow: stricture operations, prostatectomy, removal of bladder obstruction (tumor, stone, etc.), division of bands constricting the ureter or pelvis of kidney, removal of intra-uterine obstructions (strictures, valves, calculus, etc.), ligature and section of aberrant renal vessels, plastic operations upon the ureter and pelvis, nephropexy, nephrotomy, nephrolithotomy, nephrectomy, etc. To discuss the indications for any of the above operative procedures would carry one too far into the domains of surgery.

Prognosis.—In bilateral hydronephrosis the prognosis is bad. In simple unilateral uncomplicated hydronephrosis the prognosis is good. Patients with well-developed single hydronephrosis may live many years and in comfort. Complications may develop however, which may render the prognosis grave. Some of these are: Infection causing pyonephrosis, complete occlusion of the ureter by a calculus being arrested somewhere in its course, leading to pressure upon important neighboring organs, rupture into the peritoneal cavity (seldom) with resultant peritonitis. If the condition has been recognized early and the cause removed, cure may follow; but in the advanced cases the damage already done is irremediable. Spontaneous disappearance of hydronephrosis has been noted in 6 or 7 cases out of the 44 observed by Morris.

Pathology.—The effect of hydronephrosis upon the renal structure is dependent upon the character and duration of the obstructing influence. In the early stages the dilating effect is confined to the pelvis, but later on, if the causative influence is not removed, characteristic changes take place in the kidney substance proper. The dilated pelvis and kidney form an irregular, nodulated tumor mass varying in size from that of a normal kidney to an enormous tumor containing many pints of fluid. The hydronephrosis may be single or bilateral depending upon the location of the obstruction. Since the advent of ureteral catheterization, pelvic measurement and pyelography, many early cases of hydronephrosis are recognized in which the pathological changes involve only the pelvis or at most the calyces. The advantage of this is obvious, as it enables us to locate and remove the cause before irremediable damage to the kidney proper is done. The sequence of events in a hydronephrosis is as follows: First a dilatation of the kidney pelvis,

to be followed shortly by flattening, then widening of the calyces. This causes increased pressure upon the intermediate medullary substance, resulting in pressure atrophy. The more resistant capsule and fibrous tissue septa resist the increased intrarenal pressure longer than the parenchymatous substance, causing the mass to assume the lobulated or nodular appearance above described. On section, the appearance of kidney interior varies. There is noticeable an apparent atrophy of the renal parenchyma. The pyramids are more involved and sooner attacked than the cortex in the thinning-out process. The multilocular cavities, separated by septa formed by the columns of Bertini, communicate freely. In the more advanced cases these latter also disappear by atrophy, so that we have nothing left but a big thin-walled sac in which no vestige of kidney tissue is macroscopically discernible. Usually, however, traces of the septa are visible and there are some remnants of secreting substance. The cells composing the latter undergo a compensatory hypertrophy. They grow to three or four times their normal size with a corresponding increase of their functional capabilities. This is not only interesting but of importance practically. One cannot judge of the functional capability of a hydronephrotic kidney by its microscopic appearance, no matter how serious it appears; and before sacrificing a hydronephrotic kidney by nephrectomy, renal functional tests should be previously performed. Furthermore, these kidneys have their functional capability increased after operation causing the release of pressure occasioned by the retained urine. The pelvis at its place of junction with the ureter may be much distorted. The ureter is usually open, but it may be closed. The opposite kidney, if it is not itself involved, will undergo a proportionate degree of compensatory hypertrophy.

KIDNEY AND URETERAL STONE

(*Renal calculus, nephrolithiasis*)

Definition.—Kidney and ureteral stone is the formation or development within the kidney of coalesced urinary salts or solids.

Etiology.—A large amount of work, study, and experimentation has been carried out by many different investigators with the idea of determining the exact etiology of stone formation, but the results are far from conclusive and are quite contradictory. There are certain general and local disturbances which have been described as provocative of stone.

SYSTEMIC OR GENERAL FACTORS CONCERNED IN RENAL CALCULUS FORMATION.—Many factors of a systemic nature have been described as provocative of stone formation, but at most all that can be said concerning them is that they are predisposing, *e. g.*, the influence of diet.

Influence of Diet.—Sugar in the opinion of many is bad for patients suffering with a calculus or gouty diathesis, yet renal stone is extremely uncommon, according to Professor Harley, quoted by Watson and Cunningham, among women of the Turkish harems, who lead sedentary lives

and consume great quantities of sugar and sweetmeats. Similarly, gout and calculus are extremely rare among the negroes of the South who during the sugar cane season consume great quantities of sugar and sweetmeats. Some claim the ingestion of meat and large quantities of other forms of nitrogenous foods and alcoholic drinks are provocative of stone. Contradicting this claim is the experience of surgeons, who see yearly thousands of calculus cases in certain natives of India who are not only abstainers from alcoholic drinks but are also vegetarians. At most, then, diet can be claimed as a predisposing factor in stone formation, and only in certain predisposed individuals. Other general predisposing factors may be grouped under the heading of metabolic disturbances affecting the gastro-intestinal apparatus, *e. g.*, the stomach, liver, intestine, pancreas; the organs concerned in eliminating waste products, *e. g.*, the lungs, skin, lower intestines and kidneys; defective oxygenation; insufficient muscular activity; etc. Heredity and climate have also been claimed as factors.

LOCAL CONDITIONS CONCERNED IN STONE FORMATION.—The most accepted theory concerning the effect of local conditions upon stone formation is that advanced by Rainey over forty years ago. In brief Rainey's theory is that before formation of stone takes place, a colloid material formation acting as a nucleus develops, about which crystalline substance tends to coalesce and take spheroid form. This colloid substance is said to be the product of, or associated with a desquamative condition of the epithelium of the renal pelvis and calyces, etc. The weakness of this theory has been pointed out by observations which tend to show that this colloid substance exists under normal conditions. Shattuck, quoted by Cabot, says, "It has commonly been supposed that some adventitious substance is necessary to serve as a starting point, such as shed epithelium, mucus, blood-clot, bacterial colonies, or foreign bodies strictly so called, that is, introduced from without. It is one of the established facts in regard to crystallization that the genesis of crystals as distinguished from their growth takes place only in supersaturated or labile solutions. In the production of such no foreign material is necessary. It will be evident from this that in the formation of uric acid sediments as well as of calculi, the secretion of a urine supersaturated in uric acid is necessary before crystallization can occur. The presence of shed epithelium, etc., is not necessary to start it in the supersaturated fluid, and it would be quite unable to do so in the urine which was simply saturated." Cabot believes the formation of stone is largely dependent upon certain mechanical factors. It is a well-known and established fact that if a foreign body, *e. g.*, a piece of catheter, silk suture material, or a piece of stone, remains in the urinary tract to act as a nucleus, additions of urinary salts thereon will invariably occur, resulting in definite stone formation, even though the urine will be normal in every respect and there is not present supersaturation. It is also a well-known fact that crystals (sand) of sufficient size to act as a nucleus often form in the urine without stone formation. However, if the crystals are caught and retained somewhere in the urinary tract, even for a short time, stone formation may result.

This theory of Cabot's seems very plausible, and makes more easily understandable the element of heredity as a factor in stone formation.

Stones are described as primary and secondary. By primary stone is understood a stone which develops somewhere in the urinary tract free from infection. By secondary stone is understood a stone that develops somewhere in the urinary tract the seat of a morbid process, *e. g.*, pyelitis, pyelonephritis, or pyonephrosis. The type of primary stones that form in aseptic kidneys are the urate, oxylate, and cystin. Very often as a result of infection or other causes, a primary stone may have secondary deposits thereon of phosphatic or other salts, and give rise to a mixed or a laminated stone. Cabot objects to the theory of secondary stones forming as a result of infection. He admits that infection in the urinary tract is an important factor in influencing the kind of stone that forms, but does not cause its formation. He cites the well-known experience of urinary infection extending over a period of many years without stone formation. Infection by certain organisms such as the pyogenic cocci, results in the formation of alkaline urine. In such urine only phosphatic calculi develop, whereas in acid urine, uric acid, urate and oxylate calculi form. The variability in the composition may occur from time to time and affect coincidentally the composition of the urine. For example, as a result of some excretory or metabolic perversion, a uric acid stone forms; the irritation resulting from it sets up an infection with alkaline urine; phosphatic salts are now deposited upon the primary uric acid stone. Subsequently, the infection clears up, the urine returns to the normal acid reaction, and the phosphatic salts are replaced by deposits of other urinary salts like or unlike the original composition. This explains the reason for the laminated stone so often encountered.

CHEMICAL COMPOSITION.—There is much discussion in the literature concerning the most frequent type of kidney stone encountered, some claiming the uric acid and uratic stones are the commonest variety, whereas others maintain that the oxylate of calcium is the type most often seen. Statistics show that on the European continent, the uric acid and urate stones predominate, whereas in this country, the oxylate of calcium is the most common. Phosphatic stones, which are composed of the phosphates of calcium, ammonium, and magnesium are the next most common. Stones of xanthin, cystin, and indigo are rare. Stones, too, may be divided into the acid, the alkaline, and the mixed types. The acid stones are all of the above except the phosphatic variety and the mixed type is one composed of two or more of the different urinary constituents. The method and reason for the formation of the latter has already been explained. Stones consisting purely and entirely of any one urinary constituent are the exception rather than the rule.

PHYSICAL CHARACTERISTICS OF CALCULI.—Renal stones vary considerably as regards their color, consistency, surface and contour. The hardest calculi and the most irregular in type are the oxylates. They are usually dark and even black in color, having knob-like projections, on which account they are often alluded to as jackstones or mulberry calculi. Uric acid calculi are usually soft, smooth, oval and rounded,

and the color may vary from red to brown. Uratic calculi are harder than the uric acid calculi but not as hard as the oxylate. They are smooth, round or oval in shape, and the color is usually yellowish. Phosphatic calculi are chalk-like or greyish; they may be very brittle or hard, or they may be smooth but more often irregular.

As to number, they may be single or the kidney may contain as many as a thousand stones. Their size may vary from minute concretions referred to as "sand" up to a weight of $1\frac{1}{2}$ pounds (Shield's case). If the stone is single and not subjected to peculiar pressure, etc., the shape is usually round or oval. If the stones are multiple, they are apt to be faceted; certainly so, if they are in contact with each other. In operating for stone, if a faceted one is found, it indicates the existence of one or more others. If the calculus lies in the pelvis and sends branches into the calyces, the so-called stag-horn calculus is formed. Kraft, quoted by Keyes, found renal calculi forty times in 2,953 autopsies. Both kidneys were affected fifteen times. Males are more frequently affected than females. In 188 cases with renal calculus, Morris gives the ages as follows:

Under 10 years	1
Between 10 and 15 years	10
Between 15 and 20 years	20
Between 20 and 30 years	54
Between 30 and 40 years	50
Between 40 and 50 years	34
Between 50 and 60 years	17
Between 60 and 65 years	2

Symptomatology.—PAIN.—The symptomatology of kidney stone varies within wide extremes. The symptoms are not so much dependent upon the number and size of the stones as upon their location. One may see bilateral multiple calculi of unusual size presenting no symptoms and their presence revealed by accident only while examining the patient for insurance, or after x-ray study has been carried out as a part of a routine examination. On the other hand, a small pea-sized stone, shell-like in character, causing blocking at the ureteropelvic juncture may give rise to the most distressing and agonizing symptoms. Stones of the former variety are referred to as silent stones. The symptoms of the latter type are referred to as renal colic. When renal stone is confined to the region of the kidney substance, there may be no symptoms whatever (silent stone), but in about 80 per cent. of the cases a pain, dull in type and referred to the region of the kidney, will be present. The patients will refer to a feeling of soreness in the back, which may be aggravated by jolting or jumping, or there may be some costovertebral tenderness on pressure. When the stone leaves the kidneys and enters the pelvis and becomes blocked in the ureteropelvic juncture or some other portion of the ureteral canal, symptoms are produced of renal colic, which occurs at some time or other in about one-half of all cases of kidney stone. It is most often but not always itself typical. Perhaps the best description of kidney colic is that of Montaigne (Essays,

Book III, 13), who was for many years a sufferer: "Thou are seen to sweat with pain, to look pale and red, to tremble, to vomit well nigh to blood, to suffer strange contortions and convulsions, by starts to let tears drop from thine eyes, to urine thick, black, and frightful water, or to have it suppressed by some sharp and craggy stone, that cruelly pricks and tears thee." The pain when typical, comes on suddenly and without warning, at any time in the day or night, and independent of exercise, exertion, or any other provocative factor. The pain is sharp, agonizing, felt in the back rather than anteriorly, although it is surprising what a large number of cases are mistakenly diagnosed as appendicitis or biliary colic. The pain may be localized, but more often it radiates down the course of the ureter and is felt ultimately in the region of the bladder, symphysis, penis or testicle. It may produce pains exactly simulating sciatica, or the pains may be felt even in the legs or toes. Rarely the pain radiates upward toward the shoulder, and if the latter is on the right side, the diagnosis of biliary colic is more often made, whereas if the radiating pain is felt on the left side, angina pectoris is thought of. The duration of an attack varies from a momentary flash to many days of constant suffering that even morphia is powerless to calm. In some of the attacks the pain may disappear after a short time, but nausea and vomiting may persist for days or the two symptoms may be associated.

One of the striking features of renal colic, however, and a point which has much diagnostic significance, is the absence of constitutional symptoms during the attack. There is no chill or fever present, unless there is concomitant infection, and the pulse is normal in rate and volume. Urinary symptoms may or may not be present, but a consideration of the urine is of the greatest diagnostic importance. Oliguria may be present during the attack, polyuria immediately after. Urgency and vesical irritability have been described as symptoms during renal colic. But the most important urinary finding is the presence of red blood-cells in the urine. There is nothing in the opinion of the author that is more pathognomonic of renal colic than blood in the urine. It may be profuse or so slight that it is revealed only after careful microscopic examination. The author has eliminated many supposed cases of renal colic by the failure to find microscopic blood in the urine and conversely, one should hesitate to diagnose a case of appendicitis or biliary colic if the microscopic examination of the urine reveals red blood-cells. Perhaps from 15 to 20 per cent. of kidney colic cases give a previous history of an appendectomy which failed to relieve the symptoms. Albuminuria is frequently present with renal calculus, and, if infection is present, pyuria is also noted as well as cocci or bacilli. Between the attacks of renal colic, the urine may be entirely negative (15 per cent. of cases). However, in the vast majority of cases, albuminuria, pyuria or hematuria, one or all, will be found constantly present. The periods between the attacks vary greatly. A patient may have one and the only attack, or they may recur with considerable frequency.

Diagnosis.—Often the diagnosis of stone is most easy. At other times it is most difficult and one must be prepared to differentiate from it not

only every other kind of renal condition, such as infections of all sorts, mechanical or obstructive conditions, neoplasms, etc., but almost every disease that gives rise to intra-abdominal symptoms. Illustrations of some of the most common are the following: Ulcerative disease involving the stomach and duodenum, appendicitis, disease of the gall-bladder and its ducts, pathological conditions of the female generative tract, lesions of the spine, including those of the sacro-iliac joint, and disease of the central nervous system, particularly locomotor ataxia. It is surprising how often patients with renal stone have undergone previous surgical operations for removal of the appendix, ovarian or gall-bladder disease and how often the gastric crises of tabes are diagnosed only after the patients have failed to get relief following operative intervention. The above should emphasize the great importance of thoroughly investigating every intra-abdominal condition from all standpoints before deciding upon operative intervention. For example, if a simple microscopic examination of the urine were made in every case of abdominal pain, many unnecessary appendix operations would be avoided. About 20 per cent. of the patients who have had kidney stones removed by the author have had previous operations for appendicitis, gall-bladder disease, etc., done without benefit. In the vast majority of the cases this error would have been avoided if only a careful examination of the urine had been made. It has been the author's experience that in almost every case of renal colic, at least microscopic, if not macroscopic blood, will be found in the urine. This same information has been of value conversely, *viz.*, a number of intra-abdominal conditions diagnosed as renal stone have been proven erroneous by fuller study when a microscopic examination of the urine failed to reveal red blood-cells. It is important in this connection to remember that if the suspected case is in a female, the urinary examination can have significance only if the specimen is obtained by careful catheterization. If infection is associated with the stone, pus in the urine, varying with the amount of infection, is present. Albuminuria, also variable in amount, is usually present. Casts are the exception rather than the rule. Exfoliated epithelium may be noted and crystals of the type of stone present are not rare, and when present highly suggestive. Next in importance in the diagnosis of kidney stone is the x-ray. With the improved x-ray methods, it is possible to detect stones in the kidney in about 95 per cent. of the cases. On the other hand, it is well to remember that the x-ray if depended upon alone, can lead one into serious error. The latter statement needs greater emphasis when discussion of the diagnosis of ureter stone by the x-ray is considered. Various conditions, such as calcified lymph glands, phleboliths in the pelvic veins, calcified spots in the pelvic ligaments, concretions in the appendix, moles on the back, etc., may give rise to shadows suggestive of stone. On this account, it is a good rule never to diagnose renal calculus from the x-ray picture alone but only when supported by additional diagnostic data. Negative x-ray findings, even though stone is present, may be due to several factors, such as a bowel overdistended with gas and feces (avoided by previous 24-28 hour catharsis), obesity, poor x-ray technic, and the composition of the stone. Oxylate and phosphatic stones show well with

the x-ray because they are rich in lime salts, while pure uric acid and cystin stones may fail to show because they are soft and have a density comparable to the body tissues. Fortunately, however, cystin stones are extremely rare and uric acid stone is usually mixed with a certain percentage of oxylates or is covered with phosphatic salts. Having diagnosed stone, *e. g.*, by the symptoms of renal colic, urine examination and the x-ray, other essential data of great importance must now be determined. These data are: (1) The number, position, size and distribution of the stones; (2) the presence or absence of infection; (3) the functional condition not only of the affected kidney, but of the opposite kidney as well; and (4) the general physical condition of the patient.

The former three requisities are obtained by use of the x-ray, cystoscopy, ureter catheterization, wax tip bougie, bismuth bougie, pyelography, and renal functional tests (phenolsulphonephthalein, chromocystoscopy, urine-urea estimation, etc.). These methods have been sufficiently discussed in other chapters to make their repetition unnecessary. The general physical condition of the patient is obtained only after careful physical examination of the cardiorespiratory apparatus, etc., in order to obtain information which will not only afford prognostic aid, but enable us many times to exercise the proper methods of treatment and give us the correct judgment in the individual case.

Treatment.—The character of the treatment of renal calculus depends upon various factors, *viz.*: (1) Whether we have seen the patient for the first time during an attack of renal colic; (2) whether the stones are unilateral or bilateral; (3) whether infection is present or absent; (4) whether the stones are so small that they might pass spontaneously or with the aid of manipulative measures; and (5) whether the stones are too large to pass.

TREATMENT OF RENAL COLIC.—If the patient is seen during an attack of renal colic, immediate and prompt relief should be given. If the attack is not too severe and the patient's condition good, a hot **sitz-bath**, hot **water bottle**, or **turpentine stupes** applied to the kidney region may prove beneficial. But the best treatment for this condition is the **hypodermic injection of morphin**, given with a generous hand, till the condition is relieved. Massage over the region of the ureter in a downward direction has been of doubtful utility in the author's experience. The use of the **ureter catheter** to and beyond the stone with injections of **olive oil** and **cocain** around it, may displace the stone, facilitate its passage and relieve the ureter spasm, after the suggestion of Crowell. The symptoms may be so severe and distressing that the administration of **chloroform** or **ether** may be necessary. The use of the latter may not only afford temporary relief to the agonizing patient, but the author has seen it allow passage of the stone spontaneously by releasing the tight spasm of the ureter around the stone. **Papaverin** has been recommended by Macht as of great value, because it is supposed to have both an anodyne as well as a stimulative effect upon the muscular walls of the ureter. Following an attack the patient should be put upon **urinary antiseptics** for a few days and encouraged to **drink abundantly of water**. In the meantime study of the case should be carried out. During the attack of renal colic,

the possibility of anuria should be thought of and watched for. After the attack, the urine should not only be voided in a chamber, but preferably strained through gauze; otherwise the stone may be passed and missed. Some idea of how the stone is behaving may at times be gleaned by the character of the symptoms. If, however, the pain and tenderness, beginning in the loin, gradually works down the abdomen and suddenly ceases, it may be assumed that the stone has passed into the bladder, whence it can be expected as an ingredient of some urination during the next few days, or it may be revealed to the eye during a cystoscopic examination. Having rid the patient of his colic has not cured him of his stone, but for an intelligent future handling of his case, an x-ray study should be carried out, because, if it is not done, the patient may be exposed to all dangers and complications of neglected renal stone.

TREATMENT OF KIDNEY STONES—UNILATERAL.—In the consideration of this phase of the subject, items 2, 3, and 5 (see page 718) may be considered. If a kidney stone is unilateral, free of or associated with infection, and too large to pass spontaneously, providing there is no serious contraindication, *e. g.*, a serious heart or lung condition which would prevent the patient from undergoing the ordeal of a major surgical operation, removal of the stone by means of the scalpel should be the only course considered. The reasons for this position are the following: (1) If infection is not present, it is most likely to occur sooner or later, with such consequent destruction of kidney tissue that it has no functional value; (2) the dangers then to the body of an infected kidney (pus bag) have already been enumerated; (3) operation prevents these occurrences; and (4) operation prevents the occurrence of colic and the possibility of the stone being a source of constant discomfort or worry to the patient.

The type of operation will vary with conditions present. If the stone is associated with a serious destruction of the kidney so that it has little or no functional value, **nephrectomy** is the operation of choice; otherwise **nephrotomy** is indicated.

TREATMENT OF SMALL STONE—UNILATERAL.—In this type of stone, judgment concerning the proper course to pursue may be difficult. It is surprising at times, how large a stone may really pass down the lumen of the ureter and be voided. If the stone is in a kidney whose urine is uninfected and is causing no symptoms, it may be best to let it alone providing its size is not 2 cm. (.8 in.) or more in width. A larger stone than this will hardly ever pass spontaneously. The plan to pursue in this type of case will be to have the patient's urine kept antiseptic by **urotrophin** internally and **forced water by mouth** and to **roentgenograph the stone** at periodic intervals. If the stone is not showing any increase in size at these times and watching the patient's urine gives negative results, matters can be left to remain as they are. Efforts to dislodge the stone by injections through the ureter catheter of **cocainized olive oil** is a procedure worthy of trial. Even if the patient develops occasional attacks of colic, one can still pursue the policy of watchful waiting, as the author has seen stones, giving rise to periodic attacks of colic for several months, finally pass into the bladder. If however, the attacks of colic are very severe and oft-recurring, and the x-ray shows the stone immobile, opera-

tive intervention may be left to the decision of the patient. If the x-ray gives evidence that the stone is increasing in size or if the urine becomes infected, operative intervention before further damage is done had better be carried out.

TREATMENT OF STONE IN BOTH KIDNEYS.—There are many problems and different situations which it may be necessary to consider in a patient who is subject of bilateral renal calculi. If both kidneys are extensively diseased and the patient has not much pain and suffering, it may be the better part of wisdom not to subject him to the danger of an operation. If the kidneys are uninfected and in good functional condition, operation better be carried out as a preventive measure. If one kidney is in good condition and the other kidney functionless or nearly so, operation on the healthier kidney should be carried out. Nothing will be gained by working upon a useless organ, but conservation of the healthier kidney is essential. Many other more or less similar propositions will come in treating cases of bilateral renal calculi and will have to be decided according to the merits of the particular case. Medical treatment of renal calculi has only mythical value. If a patient has passed a stone, the drinking of large quantities of distilled water, careful regulation of the diet and bowels, attention to the skin exercise, etc., may be helpful in preventing the formation of future stones. But stones once formed will never be influenced by piperazin or any other drugs and the consideration of treatment is that along surgical lines as outlined above.

CALCULOUS ANURIA

Definition and Onset.—Calculous anuria is the cessation of the urinary flow due to blockage by calculus. It may be the first symptom of the calculous disease. It comes on suddenly and is due partly to retention and partly to suppression. It occurs in a variety of ways, viz.: (1) When both ureters are completely obstructed simultaneously by stone; (2) by the blocking of one ureter by stone, the other kidney being absent or destroyed, either as the result of congenital abnormality (solitary kidney, or blockage of fused ureter with two kidneys), disease (pyonephrosis, etc.), or operative removal; or (3) by the blocking of the ureter of the kidney, with the development of reflex anuria in the opposite healthy kidney (doubtful occurrence).

Symptomatology.—In the beginning of a case of calculous anuria, the patient presents the same symptomatology already described under the heading of symptoms of renal calculus. It may last for a few hours or be prolonged to days. In the treatment of the condition, the side on which the pain began aids the surgeon in his line of attack. This is next followed by the tolerant stage, in which the only symptom present is suppression of urine-anuria. The latter symptom ordinarily is not absolute; in the beginning a certain amount of urine is passed, and usually a few ounces of blood-tinged urine during the twenty-four hours. Finally, complete cessation takes place. The most remarkable occurrence in this stage is the complete well-being of the patient: he not only suffers no pain, but his health both local and general are of the best. This condi-

tion persists for between five and six days. It may be prolonged for as much as sixteen days. In this stage recovery may yet occur due to relief of obstruction. This occurred in 20.8 per cent of Morris's cases. When the latter occurrence fails, and the condition is not relieved, the patient enters the uremic stage. The uremia is of the same nature and type as the uremia due to other forms of kidney disease causing destruction of its functional capacity. The uremia usually lasts about two or three days from the first symptoms of onset, which are usually hiccoughs and vomiting. From what has been said, the importance of early diagnosis and prompt remedial treatment is self-evident.

Diagnosis.—In the diagnosis of calculous anuria, the diagnostic aids available in ordinary kidney stone are often wanting. On account of anuria, ureter catheterization may prove useless and ordinary x-ray may prove impractical on account of the serious condition of the patient. When possible however, the simple x-ray, cystoscopy, ureter catheterization, and the use of the wax tip should be employed as already outlined in discussing the diagnosis of ordinary renal calculus. When these are impractical, often sufficient data can be obtained by the physical examination of the patient. The history of preceding attacks of renal colic, tenderness in the region of the kidney on pressure, or enlargement of the kidney on palpation are important signs. The side provocative of the anuria will usually be found on the side on which the patient has colic during the premonitory stage and this is the side to attack in carrying out measures of relief.

Treatment.—The effect of expectant treatment *versus* operative treatment can be learned from the statistics of 205 cases gathered by Watson:

	<i>Cases</i>	<i>Deaths</i>	<i>Mortality</i>
Treated expectantly	110	80	72 per cent.
Treated operatively	95	44	46.3 per cent.
Total	205	124	

PALLIATIVE TREATMENT.—Prior to the introduction of the operative treatment, which alone offers chance of success, measures that are supportive and stimulative of renal function should be carried out, such as hot baths and packs, salt solution both by the Murphy method and hypodermoclysis, plenty of fluids by mouth if possible, and pilocarpin. **Massage** along the region of the ureter in the hope of dislodging the stone may be tried. **General anesthesia** of short duration may not only relieve the patient's pain if he has any, but it may also even release the stone on account of the general relaxation produced all over the body, especially in the ureter, which often is in a state of spasm.

OPERATIVE TREATMENT.—This may first be by **intravesical methods** with the catheterizing and operative cystoscope, such as removing or dislodging the stone when in the ureter. When these fail the **scalpel** may be employed. It is important to impress upon the patient and his family the gravity of the situation, even though grave symptoms are yet absent. The operation consists primarily in exposing the kidney, relieving its intense congestion, and providing an outflow of the urine by incising the

kidney (nephrotomy). If the stone is within reach and easy of removal, it should be removed at the same time, but unusual protraction of the operation by looking for stone is contraindicated. The stone can be removed later by a secondary operation, when the emergency relief has been afforded.

Pathology.—The affected kidney, either hydronephrotic or pyonephrotic, is increased to two or three times its normal size, markedly congested, has a dark purplish color and is mottled in appearance. The opposite kidney, if it is present, may show similar changes, though usually milder in degree.

CYSTS OF THE KIDNEY

Classification.—Cysts of the kidney have been classified by White and Martin, as follows: (1) Simple cysts, under which head are included small retention cysts and large serous cysts; (2) polycystic degeneration; (3) dermoid cysts; (4) paranephritic cysts; and (5) echinococcus cysts. Keyes also mentions tubercular cysts.

Multiple Small Cysts.—As the name implies, they are usually quite small, ranging in diameter, according to White and Martin, from a millimeter to a centimeter. They are usually seen in kidneys affected with chronic interstitial nephritis, and the consensus of opinion is that they are produced by the blocking up of the secretory tubules. They are located in the kidney cortex, and form projections beneath the capsule. Occasionally they occur singly. They are of no special interest except that they may possibly be confused with polycystic disease.

Large Serous Cysts.—These are also spoken of as large single cysts, solitary cysts, or hemorrhagic cysts, and are composed of several cystic cavities, containing blood or serum or both, the color of the liquid being pale or yellowish. Keyes states that the contents are never urinous. This condition is very rare, Simon having found 52 reported cases, and Brin 53. According to Herman F. Kretschmer but 48 cases have been reported since 1906. In 297 surgical diseases of the kidney, Israel found but 1 case. Albarran and Imbert have collected 31 cases, 4 of which were bilateral. Cabot's series contained 8 unilateral cysts.

ETIOLOGY.—This disease is usually found in adult life, the average age in 21 cases collected by Albarran and Imbert being forty-six years. However, it is found at both extremes, as evidenced by Rosinsky's 2 cases, one sixteen months and the other seventy-seven years of age. In Fowler's 34 cases, the extremes were four and seventy years.

It is generally conceded that it occurs more often in women than in men. According to Brin, the right kidney is more often affected than the left, and the cyst usually arises from the lower pole. There are two theories as to its origin: one, that it is a congenital malformation or the result of embryonic rests; and the other that it has the same origin as the multiple small cysts, namely, from a blocking of the uriniferous tubules in chronic interstitial nephritis. Neither theory has been proven correct.

SYMPTOMATOLOGY.—The symptoms are those of any benign growth of the kidney. When small, the patients are unaware of its existence.

When large, pressure symptoms are produced, with a sense of dragging in the kidney region. The patient may become conscious of the growth and consult a physician for this reason. Later on, digestive disturbances arise and if the tumor is very large, nutrition is interfered with, and resultant weakness and emaciation ensue. Cabot says that symptoms referable to the urinary tract are absent, as a rule, unless hematuria results from traumatism to the cyst. A case mentioned by Garceau showed definite urinary symptoms.

DIAGNOSIS.—It is difficult to make diagnosis because the signs usually are mistaken for those of hydronephrosis, ovarian cyst, or some other growth of the kidney. It is most often diagnosed at the time of exploratory operation.

TREATMENT.—Various methods of treatment have been employed such as puncture, incision and suture through the skin (marsupialization), nephrectomy, and resection. Of these, resection is the operation of choice unless the cyst wall is adherent to the larger renal vessels, or complications occur during the operation. Then nephrectomy is indicated. Some urologists prefer nephrectomy at all times, if the opposite kidney functions normally.

PATHOLOGY.—The cyst wall is thin and elastic, the color being pale or yellowish, depending upon the character of the contents. The cysts are usually of moderate size but Morris has reported one case in which the cyst contents weighed 16 pounds (6 kilograms). Cabot says that those discovered clinically are at least the size of an orange. Only a few reach a size large enough to be discovered during life. These cysts may be multiple, but when they are, one is usually much larger than the others. As a rule, the cyst is located in the cortex and according to Cabot, when arising in the parenchyma, it rarely opens into the pelvis. The wall may undergo a cartilaginous change and have various salts deposited in it. When bleeding occurs into the sac, the cyst is spoken of as hemorrhagic. The cyst wall is firmly adherent to the kidney tissue and sometimes to the surrounding viscera, making it difficult of removal.

Polycystic Degeneration.—This disease is characterized by a conversion of the kidney (nearly always bilateral) into a large number of cysts, the intervening normal tissue being scant in quantity.

ETIOLOGY.—Several theories have been advanced as to its causation. Some think it is due to inflammation and plugging of the tubules with resultant cyst formation; others believe it to be due to congenital malformation, while still others believe that they are cyst adenomata. There is no convincing evidence to support any one theory, but occlusion of the tubules certainly plays an important part.

The disease may occur at any age, but most cases occur after forty and practically nine between the ages of one and twenty-one years. It has been known to develop to such an extent during intra-uterine life as to interfere with labor. Cabot's collected statistics show the greatest number of cases between the ages of forty and sixty. The disease has been classified into congenital and adult types but there is no essential difference between the two.

It is slightly more prevalent in females than in males, but there is no marked difference. It is practically always bilateral, but 9 unilateral cases having been found by Seiber. However, it progresses more rapidly on one side than on the other. It has been known to occur in various members of the same family, but heredity is not an important causative factor.

ASSOCIATED LESIONS.—This condition is frequently associated in adults with cyst formation in the liver. Cardiac hypertrophy and arteriosclerosis are frequent concomitants. In the congenital form all sorts of malformations have been found associated, such as cleft palate, imperforate anus, cysts of the ovary, supernumerary digits, talipes, etc.

SYMPTOMATOLOGY.—The disease runs a course, with symptoms similar to those of chronic interstitial nephritis, unless the tumor becomes noticeable because of its size. There is local pain and tenderness, at first unilateral, later bilateral. The dull aching pain is due to distention of the renal capsule, while the paroxysmal attacks of colic are due to the passage of clots. Hematuria may occur. Later on, symptoms of kidney insufficiency develop and finally uremia. The changes in the urine are those of interstitial nephritis. Tumor, pain, and hematuria are the surgical symptoms present.

DIAGNOSIS.—This is very difficult because it is an insidious growth, and resembles so closely in symptoms chronic interstitial nephritis. Statistics show, that very few are diagnosed during life. If, however, bilateral knotty renal tumors are discovered, with the signs and symptoms of chronic interstitial nephritis or uremia, the true nature should be suspected. Renal functional tests are of great value, especially relative renal excretory functional tests. If the tumor is unilateral, it is very hard to diagnose, as malignancy is at once suspected. Pyelography will help to distinguish the condition from solid tumors and in determining the true condition. The author has been able to diagnose before operation 2 cases seen by him. It is also to be differentiated in diagnosis from the various other kidney cysts and pyo- and hydronephrosis.

TREATMENT.—The treatment is that of chronic interstitial nephritis, unless conditions are favorable to operation or symptoms and complications call for special treatment. Pelvic lavage may control bleeding. Nephropexy may be beneficial, if the size of the growth has caused the kidney to become movable with resultant kinking of the ureters. Decortication has been tried to prevent alarming uremic symptoms but is ineffective. **Rovsing's operation** or **puncture of the larger cysts** is said by most authorities to be the operation of choice, as it relieves compression and helps to prevent the formation of new cysts by relieving obstruction. Partial nephrectomy may be tried if the growth is limited to one portion of the kidney, but the cause of its limited application and frequent failure is evident. **Total nephrectomy** is indicated if there is uncontrollable hemorrhage, or if the function of one kidney is practically or entirely destroyed, the other kidney being fairly normal. The bilateral nature of the disease limits its scope and the mortality is high.

PROGNOSIS.—This depends upon the rate of cyst formation and the relative involvement of each kidney. If unilateral, the patient may live

for years. The age of onset also plays an important part, intra-uterine cases resulting in death soon after birth and infantile patients living only a short time. Death is usually due to uremia or some terminal infection.

Duration.—According to Morris, adults survive from one to ten years. One patient lived twenty-two years after diagnosis. Boinet and Rebaud state that 50 per cent. of children congenitally affected die immediately after birth.

PATHOLOGY.—Grossly one sees a large number of cysts scattered throughout the kidney and just beneath the capsule, causing the surface to appear very irregular which latter characteristic is said by Keyes to be so striking that it is all but pathognomonic of the disease. With the exception of the knobby appearance of the surface, the general contour of the kidney is more or less preserved. Occasionally one cyst is so much larger than the others that this is not true. The tumor may reach enormous proportions as evidenced by Morris's case, in which the tumor weighed 16 pounds (6 kilograms). In the average case, however, the kidney is several times its normal size. The color varies, depending in a large measure upon the nature of the cyst contents. The latter may be liquid, viscid, serous, or colloid. Cabot says that the cystic contents may be urinous, but Keyes denies this. The larger cysts may be dark and hemorrhagic. The walls of the cysts are separated by abnormal kidney parenchyma or fibrous tissue. Microscopically, the cyst wall is lined with flattened epithelium, which in places has proliferated, causing projections into the cyst cavity. The tubules and malpighian capsules are seen in various stages of cyst formation.

Dermoid Cysts.—These are extremely rare, and differ in no respect from similar cysts in other parts of the body. The cyst is composed of hair and a material containing epithelium and products of degeneration. The diagnosis can be made only by the passage of hair in the urine or by section of the cyst. Nephrectomy gives the only relief.

Paranephritic Cysts.—These are usually the result of perinephritic hematmata which have become encapsulated. They may be hydatid in nature, or according to White and Martin, they may be the result of embryonic rests. They may arise from the capsule of the suprarenal gland. They are unilateral and single and produce symptoms only because of their size. Malignant changes may occur, particularly sarcomatous. Excision of smaller growths is easy but considerable difficulty may be encountered with the larger ones.

Echinococcus Cysts.—**ETIOLOGY.**—Hydatid cyst is the cystic stage in the life cycle of a cestode, known as the *tinea echinococcus*. This condition is not often encountered in this country; it is not uncommon in Europe, but quite common in Australia and the Argentine Republic and is extremely prevalent in Iceland. In the latter country 16 per cent. of the population is supposed to be infected. The eggs are ingested with food and water, hatch into embryos in the stomach and intestines, and by means of hooklets burrow into the walls of the stomach or gut, whence they enter the venous system. This explains the apparent predilection of the disease for the lungs and liver, as the blood reaches these organs

before it passes on to the kidney. Edward L. Young, Jr. states that the relative proportion of kidney cases to all others is as 1 is to 5, while White and Martin state that from 5 to 8 per cent. of all cases occur in the kidney. The condition may be found at any age, but most cases occur in adult life. It shows no preference for either sex and is usually unilateral, the left kidney being nearly always the one affected. The disease begins in the cortex just beneath the capsule, but any portion of the kidney may be later involved. It has been known to have its origin in the perirenal tissue. The cyst wall is composed of two layers, an outer or hydatid, and an inner or germinal. In the fluid contents are found the hooklets. Around the cyst wall is dense fibrous tissue formation with no definite line of demarcation. The cyst grows slowly, as a rule, and the kidney tissue undergoes compensatory hypertrophy so that the condition may exist for years without alarming symptoms. Trauma may produce suppuration in the cyst and general pyemia may follow.

SYMPTOMATOLOGY.—When small, there may be no symptoms. When of large size, unless the cyst ruptures, the symptoms are those produced by weight and pressure, namely, a sense of aching and dragging in the kidney region. Acute pain is not often present. Pressure on the surrounding organs, such as stomach or gut, may cause only mild digestive disturbances, but occasionally symptoms of intestinal obstruction. Rupture into the surrounding viscera causes pyonephrosis with its resultant symptoms, and rupture into the kidney pelvis causes renal colic and nearly always hematuria. The ureters may become blocked, causing hydronephrosis. Rupture into the peritoneum causes mild peritonitis, as a rule, and urticaria or severe anaphylactic reaction. Occasionally the tumor is discovered accidentally by the patient.

DIAGNOSIS.—Bismuth x-rays will differentiate this condition from other abdominal tumors and radiographs of the kidney will show its connection with that organ. It is ordinarily mistaken for hydronephrosis or ovarian cyst but hypernephroma and polycystic kidney may be confused with it. A fixation test, described by Lamboy and Parver, is supposed to be specific. The use of the x-ray and the measuring of the capacity of the renal pelvis will rule out hydronephrosis. Hydatid thrill is rarely obtained. After rupture into the pelvis a positive diagnosis can be made by finding the hooklets in the urine. Eosinophilia is usually present.

TREATMENT.—As soon as the disease is diagnosed, operation should be advised, its nature depending upon conditions encountered. If the process is limited, with no complications, resection may be the operation of choice. White and Martin recommend aspiration of the cyst, followed by injection of a 5 per cent. formaldehyd solution, and a few minutes later dissection of the cyst wall and closure of the remaining cavity by suture. If suppuration is present, they recommend drainage. Edward L. Young, Jr. prefers marsupialization in all of the very large cysts and some of the smaller ones, stating that it is simplest and safest and in the end gives good results. If the kidney substance is extensively involved or destroyed, nephrectomy is the operation of choice.

PROGNOSIS.—The disease may be harmless or terminate fatally. Occasionally, spontaneous recovery follows rupture into the pelvis or the cyst may die. This however is rare. Rupture into the surrounding organs or peritoneum is a serious complication.

Tabercular Cysts.—These occur during the course of kidney tuberculosis, and are dealt with in the chapter on kidney tuberculosis.

RENAL TUMORS

Introductory.—Primary tumors of the kidney, although somewhat rare as compared to tumors originating in other organs and tissues of the body, are none the less important and of great clinical interest. Metastatic tumor growths in the kidney are quite common but ordinarily are not recognized until the primary growth is well advanced. It has been estimated that from 0.8 to 1 per cent. of malignant tumors originate in the kidneys and a much smaller percentage of benign tumors occur in this organ. Malignant renal growths are unique in that a fairly large proportion occur in children. Considerable controversy as to the exact pathological nature and origin in the embryonic structures of some of these tumors is still in progress. Although such exact knowledge of the origin of these malignant tumors is of great pathological interest, it is not so essential to the general practitioner and surgeon whose chief objects are early recognition and effective treatment. That classifications of renal neoplasms are unsatisfactory is evidenced by the great number and variety of classifications. The following is a list of renal growths divided into two groups according to their clinical behavior:

Benign Growths

Adenoma
Fibroma
Lipoma
Angioma
Papilloma

Malignant Growths

Hypernephroma
Carcinoma
 Adenocarcinoma
 Papillary Carcinoma or Papillary Epithelioma
 Squamous-cell Carcinoma or Epithelioma (Nonpapillary)
Sarcoma
 Round Cell
 Spindle Cell
Embryonic Tumors
 Teratoma
 Rhabdomyoma
 Mixed Tumors

BENIGN RENAL TUMORS

Classification.—The most important feature of benign kidney growths is their strong tendency to undergo malignant changes. With the exception of benign growths situated in the kidney pelvis they do

not give rise to any symptoms and hence are recognized only accidentally during operation or at autopsy.

ADENOMATA.—They are quite rare in the kidney. They appear as grayish-red nodules in the cortex; sometimes they attain large size, but usually remain small. Microscopically they are seen to be composed of ramifying tubular or glandular structures lined with epithelial cells similar to those of the convoluted tubules.

FIBROMATA.—These are usually small and appear as firm, round, grayish nodules displacing renal tissue in the cortex or pyramids. Microscopic examination shows an atypical fibrous tissue and often an admixture of smooth muscle.

LIPOMATA.—These are rare in the kidney. They are usually quite small and situated under the capsule. In addition to the fat these tumors often show smooth muscle and other elements.

ANGIOMATA.—These are very rare in the kidney. They are usually situated below the capsule and remain quite small. Occasionally they may originate in the renal pelvis. The most generally accepted theory as to their origin is that of Ribbert, namely, that they grow independently from a rudiment which is destined to form blood-vessels.

PAPILLOMATA.—Although they are in the beginning certainly benign and usually classed as such, they show a strong tendency to become malignant and are then papillary carcinomata. They are the commonest tumors of the renal pelvis, and may be single or multiple. Usually they are unilateral, but they may be bilateral. These tumors originate in either the mucosa of the kidney pelvis or in that of the ureter. Papillomata originating in the kidney pelvis often spread to the ureter, or *vice versa*. Like papillomata of the bladder these tumors tend to recur after removal and finally become carcinomata. Grossly, papillomata appear as branching soft tufts composed of numerous delicate villi closely packed together. Microscopically, the villi are seen to have a central blood-vessel which is surrounded by the typical stratified epithelium of the renal pelvis. The cells are held together by loose connective tissue.

Symptomatology.—When situated within the renal parenchyma, benign tumors, unless they attain large size, are symptomless, and therefore are of no importance surgically. When of large size, the tumor will produce pressure symptoms,—pain, edema, varicocele, and gastro-intestinal disturbance. However, when located in the kidney pelvis, these tumors frequently give rise to symptoms. Angiomata may rupture and result in serious hemorrhage.

Papillomata bleed intermittently but ordinarily the hemorrhage is not large. Pain may or may not accompany hematuria, but when large clots are passed, colicky pain occurs. The growth together with a clot may fill the entire pelvis and obstruct the ureter, giving rise to a hema-tonephrosis. A tumor may then be palpated and the patient will have pain due to pressure.

Diagnosis.—Inasmuch as the symptoms when present at all are the same for the most part with benign as with malignant tumors of the

kidney, it is practically impossible to distinguish between them before operation. Slow growth and less marked symptoms are features which may give one the impression that a given tumor is benign. Of course in the late stages of malignancy with metastases and cachexia, the diagnosis is quite evident, but it is also too late to be of much benefit to the patient. Benign tumors producing symptoms are dealt with in the same manner as malignant tumors so that from the standpoint of treatment it is not a matter of great importance to distinguish them before operation. The same diagnostic methods apply in the diagnosis as will be mentioned under malignant tumors.

Treatment.—The diagnosis of renal tumor demands nephrectomy. This procedure is warranted with tumors which apparently are benign, not only to completely relieve symptoms, but also because of the very strong tendency to malignant transformation.

MALIGNANT RENAL TUMORS

Classification.—The so-called hypernephromata are by far the most important and the most frequent tumors of the kidneys. In adults these growths greatly outnumber any other; in children the embryomata compose the larger proportion. An idea of the relative frequency of the different types of malignant growths may be obtained from the following reports. Garceau in a study of the surgical and autopsy material for ten years at the Massachusetts General Hospital and Boston City Hospital reports the following:

Perirenal sarcoma	1
Papilloma of renal pelvis	1
Hypernephromata of renal parenchyma (large)	33
Hypernephromata of renal parenchyma (small)	12
Carcinomata of renal parenchyma	3
Papillary cystadenomata of kidney parenchyma	4
Papillary adenomata of kidney parenchyma	11
Sarcoma of kidney parenchyma (round cell)	1
Sarcoma of kidney parenchyma (spindle cell)	1
Fibromata	14
Lipomata	5
Total	86

Hypernephromata thus make up 52.33 per cent. of all renal growths in this list. Excluding the tumors which are definitely benign, hypernephromata compose 68.17 per cent. of the malignant growths.

Louis B. Wilson in a study of 92 tumors at St. Mary's Hospital, Rochester, Minn., reports the following:

Hypernephromata or mesotheliomata	71
Embryomata	3
Wolffian tumor	1

Sarcomata	7
Adenoma	1
Fibroma	1
Papillomata of renal pelvis	3
Carcinomata of renal pelvis	4
Squamous-celled epithelioma	1
<hr/>	
Total	92

In this list hypernephromata make up 77.17 per cent. of all tumors. Owing to the difference of opinion among various authors as to the criteria of classifying these tumors there are diversities in different tables. For this reason many reports, especially the older ones, are of little value in studying the frequency of the types. The above figures perhaps give one a correct impression of the proportion of each variety of renal growths as they are at present classified.

HYPERNEPHROMATA.—The term hypernephromata is applied to a group of tumors which according to Grawitz originate in small misplaced masses of adrenal tissue (adrenal rests) which are so frequently found imbedded in the substance of the kidney. Before Grawitz directed attention to these tumors they were variously grouped as lipomata, sarcomata, or carcinomata. The theory of origin from adrenal rests has received very general approval, but from time to time numerous other theories have been advanced. A theory which recently has been gaining favor is that presented by Louis B. Wilson, who contends that these tumors develop from islands of nephrogenic tissue which have failed to connect with the renal pelvis. He accordingly applies the term "mesotheliomata" to these tumors.

Grawitz presented the following five reasons for his conclusion: (1) The position of these tumors underneath the capsule where adrenal rests are often found normally; (2) cells are singular in type to adrenal cells; (3) characteristic fatty infiltration of the cells which is never found in the kidney epithelium; (4) the presence of a limiting capsule; and (5) the arrangement of the cells in relation to the stroma similar to that of adrenal cortex.

The following reasons as stated by Stoerck are presented to disprove the theory of Grawitz: (1) The Grawitzian tumors most frequently develop at the lower pole of kidney, where adrenal rests are not found; (2) the so-called fat of the cells of the Grawitzian tumors is usually not fat, but a vacuolation related to the glycogen content of the cells; (3) the Grawitzian tumor is a tumor of the renal cortex and not of the renal capsule in which the adrenal rests are usually found; and (4) the Grawitzian tumors almost invariably contain tubules the analogues of which are never seen either in the normal suprarenal or in tumors of that gland.

Stoerck suggested that these neoplasms arise from regenerating convoluting tubules in the atrophic kidney.

Glynn adds the following reasons to disprove the adrenal origin of these tumors: (1) Histologic dissimilarity between tumors of the kidney and adrenal gland; (2) renal tumors never influence growth of sexual characteristics; and (3) why should adrenal rests, though comparatively rare in the kidney, produce hypernephroma, the commonest renal tumor, while adrenal rests in other localities though comparatively common so rarely produce tumors either benign or malignant?

At present it may be stated that hypernephromata comprise a group of tumors which are peculiarly different in their histological characters from other tumors and stand out in a separate group. Their exact origin is still unsettled. Clinically, however, these tumors are well understood.

Hypernephromata vary in size and may be situated in any other part of the kidney. The larger growths compress and distort the normal renal tissue. They appear usually as soft, yellowish nodules which may vary from a very minute size to the size of an adult head. Less frequently they are brownish or grayish due to secondary changes. Ordinarily they are encapsulated, but in the later stages of development the capsule may rupture, and the growth spread into contiguous structures.

A cut section shows a glistening yellow surface and in the larger tumors grayish areas of necrosis and cystic cavities filled with blood. Microscopically the tumor is seen to consist essentially of large polygonal or cubical pale transparent cells and small nuclei, resembling closely the cells of the adrenal cortex. The cells are held together by a fine stroma in which there are numerous thin-walled blood-vessels. A striking feature is the situation of cells directly upon the capillary walls. Usually the cells have an alveolar arrangement; less frequently a papillary formation is observed.

These growths metastasize almost exclusively through the blood stream. Frequently specimens are observed with the growth extending directly into the renal vein. Metastases may be disseminated in all parts of the body. The most frequent locations of metastases, however, are the lungs and long bones. Although some hypernephromata remain small and never metastasize, as shown by the incidental discovery of such growths at autopsy, it is nevertheless desirable to consider the entire group malignant.

CARCINOMATA.—These are distinctly tumors of adult life, being rare before the fourth decade. According to the present standards of classification true carcinomata compose only a small percentage of renal tumors. Formerly many growths now designated as hypernephromata were placed in this group. Carcinomata of the parenchyma have their origin in the tubular epithelium. Metastasis occurs through both the blood and lymphatic circulations.

Due largely to early metastasis the primary growth seldom attains large size and the kidney is not much distorted. There are often areas of necrosis, hemorrhage or cyst formation. Grossly these tumors have no very characteristic appearance. Microscopically they are seen to consist of rather large irregularly shaped epithelial cells with granular cytoplasm and large nuclei containing several nucleoli. The cells are

held together by a connective tissue stroma. In many specimens the cells are found in irregular groups without any definite arrangement. In other specimens the cells are arranged in strands.

ADENOCARCINOMATA.—These tumors represent the malignant stage of adenomata and by many are termed "malignant adenomata." They often are of large size. Some of the alveolar spaces are filled with cystic fluid. Within such cysts the epithelium may be thrown up in papillary folds, and the growth may be termed papillo-adenocarcinoma, or papillary adenocystoma.

PAPILLARY CARCINOMATA (PAPILLARY EPITHELIOMATA).—These tumors occur in the renal pelvis and represent the malignant stage of the simple papillomata. They seldom attain very large size on account of the early accompanying profuse hemorrhage.

SQUAMOUS-CELL CARCINOMATA (NONPAPILLARY EPITHELIOMATA).—These originate in the mucosa of the renal pelvis or ureter. They cause hematuria and give rise to hematuria.

SARCOMATA.—These are chiefly of the round-cell or spindle-cell variety. Although not so rare, they are not so common as other varieties of malignant growths. In Garceau's collection of 86 renal growths, there are 2 sarcomata, round-cell and spindle-cell. They originate chiefly in the fibrous tissue of the renal cortex. Usually they are comparatively small, uneven, soft grayish masses. Metastases occur through the blood stream.

TERATOMATA, RHABDOMYOMATA AND MIXED TUMORS.—These are closely related and are often grouped as embryonic tumors. They are distinctly tumors of childhood. Binney in a collected series of 114 cases of renal growths reports 27 embryomata. Their origin is still a subject of controversy. The general opinion, however, is that they originate in an isolation of a blastomere in the developing embryo, resulting in a displacement of tissue normally found in other regions of the body. Such growths often attain very large size, weighing as much as 6 pounds (2.2 kilograms). The gross appearance is quite variable.

Teratomata contain tissues representing all three germinal layers. Thus skin and its appendages, teeth, convoluted structures resembling intestine, cartilage and thyroid tissue may be found. Although teratomata are benign, it is not at all uncommon for carcinoma to develop at some point in their epithelium (MacCallum). Dermoid is a simple form of embryonic growth composed chiefly of epithelial structures.

Rhabdomyomata are composed essentially of muscle fibers but usually also have an admixture of other supporting tissue elements as cartilage and connecting tissue, and sometimes epithelium. Mixed tumors are composed of an agglomeration of various kinds of cells: Epithelial cells in glandular formation, about which are striated and unstriated muscle fibers, connective tissue, cartilage and often sarcoma tissue. They grow rapidly and metastasize through the blood stream.

COMBINED TUMORS.—In the same kidney two or more growths of entirely different types may be found. Graves and Templeton recently reported two such cases and reviewed the literature. One case showed

papillary carcinoma in the pelvis and hypernephroma. The other case showed papilloma of renal pelvis and papillary cystadenoma of kidney.

Etiology.—AGE.—The extremes of age, under five years and over forty years are the periods of renal malignancy. This is well shown in Koster's table as shown by Keyes:

From birth to 5 years	128 cases
Six to ten years	41 cases
Forty to fifty years	125 cases
Over fifty years	128 cases

Total 422 cases

SEX.—Most writers state that males are affected more often than females. No explanation for this difference, however, is stated. Of 74 cases reported by Barney, 43 were in males and 31 in females. In a study of 83 cases, Braasch found 62 per cent. in males.

Heredity and trauma are not causative factors. Trauma, however, may excite hemorrhage in a tumor that was previously symptomless. Chronic infections and calculi in the renal pelvis are the effects rather than causative factors in renal tumors. Both kidneys are about equally affected.

Symptomatology.—Hematuria, pain and tumor are the three classical symptoms of renal tumor. Only one symptom may be present for a long period. When all are present, the new growth is well advanced and perhaps so far as to preclude the possibility of cure. Hinman found all three of these symptoms present in an average of 38 per cent. of cases at the time the patients presented themselves for treatment. In a study of 83 cases Braasch found as the first symptom hematuria in 47 per cent., pain in 32 per cent. and tumor in 15 per cent.

Hematuria is the most important single symptom. Ordinarily, in the beginning at least, hemorrhage is not large and may be just sufficient to tinge the urine. In some cases, however, hemorrhage is large and clots may fill the pelvis and ureter giving rise to renal colic. The blood appears spontaneously, lasts several days and may not be noticed again by the patient for months or even years. Unfortunately this complete spontaneous disappearance of the symptoms often serves to reassure the patient and proper investigation is deferred. Hematuria always demands a most thorough examination of the urinary tract. In children hematuria is not very frequent.

Pain is quite variable in character, location, intensity and duration. The growth itself or an obstruction of the ureter with filling of the pelvis may press upon nerves and nerve-endings, resulting in pain often of the dull aching character. The pain may be situated in the loin on the affected side or be referred to abdomen or opposite side. Pain due to passage of a clot through the ureter is of the colicky variety and is referred to the affected kidney region and groin.

Renal tumors in children usually are not recognized until a palpable mass makes its appearance. The tumors which are chiefly of the

embryonal type grow rapidly and attain large size, making them readily palpable in the hypochondrium. In adults a tumor is not palpable until the new growth is well advanced. Even when of fairly large size a renal tumor is not often palpable, especially in persons with thick abdominal walls. A mass due to renal tumor appears in the upper abdomen just to one side of the midline. The tumors vary in size and consistency. They may feel hard and nodular or soft and smooth. Before the growth has extended outside the kidney the tumor is movable; after extension into adjacent structures the mass is firmly fixed and usually the condition is then inoperable. A renal mass due to pelvic new growth with hematonephrosis may be intermittently palpable, as pointed out by Israel. When not palpable by bimanual palpation in the prone position, renal tumors can sometimes be felt with the patient in the lateral position.

URINARY FINDINGS.—During active hemorrhage blood is readily recognized in the urine. Microscopic blood may be found when no other symptoms are present. In some cases pus cells are found, due to an accompanying inflammatory process. Barney has recently reported a case in which inflammatory symptoms (fever, leukocytosis and pyuria) entirely overshadowed the symptoms of tumor.

PRESSURE SYMPTOMS.—Due to compression of the spermatic vein, particularly when the tumor is on the left side, varicocele of large size may appear. Pressure upon the large veins within the abdomen in the late stages causes ascites and edema of the lower extremities. A right-sided tumor or extension to the liver may result in jaundice. Severe neuralgia may be caused by pressure upon nerves. Intestinal obstruction may be caused by a large tumor.

Gastro-intestinal disturbances as anorexia, indigestion, constipation or diarrhea are sometimes prominent symptoms. Fever, usually of moderate degree, is present in a small percentage of cases. In the late stages anemia and cachexia develop.

Diagnosis.—The diagnosis must be made early if one is to hope for cure of these cases. It is well recognized that early diagnosis is quite difficult and at times impossible, due to lack of symptoms or to the vague indefinite nature of the symptoms. Often the symptoms are mild for a time and disappear spontaneously so that the patient and sometimes the physician feels assured that no serious trouble exists. At present, however, we possess certain exact methods of investigating the urinary tract and it is only by utilizing these methods in cases that present the slightest suspicion of renal tumors that we can make early diagnosis. The typical late cases presenting all the classical symptoms, hematuria, pain of the characteristic type and tumor, are readily recognized.

Cases presenting one or more of the symptoms suggesting renal tumor should be investigated by urinalysis, cystoscopy and catheterization of ureters, pyelography, and radiography.

In complete urinalysis, careful urine examination may show red blood-cells, pus cells and albumin.

In cystoscopy and catheterization of ureters, more information will be obtained if cystoscopic examination is made during the period of

hematuria. The ureter opening on the affected side may be congested and irregular in appearance. Blood may be seen issuing from the ureter opening or a blood-clot may be protruding from the ureter. Blood in specimens obtained by ureteral catheters may be entirely of traumatic origin, due to introduction of catheters and has no diagnostic value.

Catheters should be introduced into both ureters and the functional capacity of each kidney determined by phenolsulphonephthalein or other methods. There may be marked impairment or no function on the affected side due to destruction of renal tissue or obstruction of the pelvis and ureter with a clot. In early cases there may be no impairment of function on the affected side.

Pyelography is of paramount importance in the diagnosis of renal tumor. By this procedure the characteristic changes in the renal pelvis can be observed. The chief deformities noted are: Retraction of one or more calyces producing the so-called "spider leg" deformity, irregular pelvic dilatation, dilatation of the upper ureter, or the position of the pelvis may be changed.

Radiography may show the outline of the mass, and the presence or absence of calculi.

The diagnosis as to the type of malignant renal growth is quite impossible before operation. The following conditions are to be differentiated from renal new-growth by the proper methods: Renal calculus, renal tuberculosis, essential hematuria, hydronephrosis, floating kidney, tumor of spleen, tumor of liver, tumor of pancreas, tumor of intestine and tumor of ovary.

Treatment.—Early nephrectomy is the only treatment. This procedure is to be advised if the unaffected kidney is sufficient to maintain life, providing the tumor is removable and providing there are no metastases. Operation, however, is sometimes performed to relieve pain in cases beyond hope of cure. After nephrectomy radium and x-ray therapy may be employed in the hope of preventing recurrence.

Course and Prognosis.—Renal malignancy without operation is inevitably fatal. The course especially of hypernephromata is often slow. In Garceau's cases the average duration of symptoms of hypernephromata was two years and three months.

Carcinomata and sarcomata may run a much more rapid course. After careful removal of the tumor by operation one can never be certain that the growth will not recur.

BIBLIOGRAPHY

Pyelitis

CABOT, H., AND CRABTREE, E. G. A classification of renal infection with particular reference to treatment. *Bos. Med. & Surg. Jour.*, 1916, clxxiv, 780.

— Colon bacillus pyelonephritis: Its nature and possible prevention. *Trans. Section. Gen.-Urin. Diseases, A. M. A.*, 1916, lxvii, 209.

CASPER, L. *Genito-Urinary Diseases*, 1906, P. Blakiston's Son & Co., Philadelphia.

- CHETWOOD, C. H. Practice of urology, 1921, p. 603, W. Wood & Co., New York.
- CRABTREE, E. G. Observations on the etiology of renal infection. *Lancet-Clinic*, 1916, cvi, 99.
- EISENDRATH, D. N., AND KOHN, J. V. Rôle of lymphatics in ascending renal infection of the urinary tract. *Trans. Section Gen.-Urin. Diseases, A. M. A.*, 1916, lxvi, 561.
- GERAGHTY, J. T. The treatment of chronic pyelitis. *Trans. Section Gen.-Urin. Diseases, A. M. A.*, 1914, p. 113.
- KELLY, H. A., AND BURNAM, C. F. Diseases of the kidneys, ureters and bladder, Vol. II, p. 219, 1914, D. Appleton & Co., New York.
- KEYES, E. J., JR. Diseases of genito-urinary organs, p. 367, 1912, D. Appleton & Co., New York.
- KOLL, I. S. The experimental effect of the colon bacillus on the kidney. *Trans. Section Gen.-Urin. Diseases, A. M. A.*, 1914, p. 104.
- KRETSCHMER, H. L. The treatment of pyelitis. *Surg., Gyn. & Obstet.*, 1921, xxxiii, 632.
- KRETSCHMER, H. L., AND HELMHOLZ, H. F. The treatment of pyelitis in infancy and childhood. *Jour. Amer. Med. Assoc.*, 1920, lxxv, 1303-5.
- OSLER, SIR WM. Practice of medicine, p. 681, D. Appleton & Co., New York.
- QUINBY, W. C. Pyelitis in children. *Trans. Gen.-Urin. Section, A. M. A.*, 1916, lxvii, 218.
- WATSON, P. S., AND CUNNINGHAM, J. H. Genito-urinary diseases, 1908, Lea & Febiger, Philadelphia.
- WHITE AND MARTIN. Genito-urinary and venereal diseases, p. 626, 1920, J. B. Lippincott Co., Philadelphia, Pa.

Hydronephrosis

- BRAASCH, W. F. Perienphritic abscesses. *Surg., Gyn. & Obstet.*, 1915, xxi, 631.
- CABOT, H. Urology, Vol. II, p. 432, 1918, Lea & Febiger, Philadelphia, Pa.
- CABOT, H., AND CRABTREE, E. G. Frequency of recurrence of stone in kidney after operation. *Surg., Gyn. & Obstet.*, 1915, xxi, 223.
- Colon bacillus pyelonephritis: Its nature and possible prevention. *Trans. Section Gen.-Urin. Diseases, A. M. A.*, 1916, lxvii, 209.
- CASPER, L. Genito-urinary diseases, 1906, P. Blakiston's Son & Co., Philadelphia, Pa.
- CAULK, J. R. Ureter catheter drainage in the treatment of renal infections with special reference to the infected hydronephrosis complicating pregnancy. *Jour. Amer. Med. Assoc.*, 1917, lxviii, 675.
- CHETWOOD, C. H. Practice of urology, 1921, Wm. Wood & Co., New York.
- CRABTREE, E. G. Some operations on the etiology of renal infections. *Lancet-Clinic*, 1916, cvi, 99.
- GERAGHTY, J. T. The treatment of chronic pyelitis. *Jour. Amer. Med. Assoc.*, 1914, lxiii, 2211.
- HINMAN, F. Urinary antisepsis: A clinical and bacteriologic study. *Jour. Amer. Med. Assoc.*, 1915, lxxv, 1769.
- KEYES, E. L., JR. Diseases of the genito-urinary organs, p. 505, 1910, D. Appleton & Co., New York.
- KOLL, I. S. The experimental effect of the colon bacillus on the kidney. *Trans. Gen.-Urin. Section, A. M. A.*, 1914, lxii, 104.
- KRETSCHMER, H. L. Pyelitis follicularis. *Surg., Gyn. & Obstet.*, 1913, xvii, 612.
- KRETSCHMER, H. L., AND HELMHOLZ, H. F. The treatment of pyelitis in infancy and childhood. *Jour. Amer. Med. Assoc.*, lxxv, 1920, 1303.
- QUINBY, W. C. Pyelitis in children. *Trans. Gen.-Urin. Section, A. M. A.*, 1916, lxvii, 218.
- WATSON, P. S., AND CUNNINGHAM, J. H. Genito-urinary diseases, 1908, Vol. II, p. 1129, Lea & Febiger, Philadelphia, Pa.

WHITE AND MARTIN. Genito-urinary surgery and venereal diseases, 1920, p. 505, D. Appleton & Co., New York.

Cysts of the Kidneys

- CABOT, H. Modern urology, 1918, p. 650, Lea & Febiger, Philadelphia, Pa.
 CHETWOOD, C. H. Practice of urology, 1921, p. 554, Wm. Wood & Co., New York.
 KEYES, E. L., JR. Genito-urinary diseases, 1905, p. 545, D. Appleton & Co., New York.
 KELLY AND BURNAM. Diseases of the kidneys, ureter, and bladder, 1914, Vol. II, p. 367, D. Appleton & Co., New York.
 WHITE AND MARTIN. Genito-urinary and venereal diseases, 1905.
 YOUNG, E. L., JR. The chemical and pathological evidences of the possibilities of spontaneous healing of renal tuberculosis without total destruction of the kidney. Jour. Amer. Urol. Assoc., Brookline, 1916.

Renal Tumors

- BARNEY, J. D. Malignant diseases of the kidney with unusual symptoms. Bos. Med. & Surg. Jour., 1920, clxxxiii, 710.
 ——— The symptomatology of renal tumors: A study of 74 cases from Massachusetts General Hospital, Boston Med. and Surg. Jour., clxviii, 1913, 300.
 BERG, A. A. Malignant hypernephroma of the kidney: Its clinical course and diagnosis with a description of the radical operative cure. Surg., Gyn. & Obstet., 1913, xvii, 463.
 BINNEY, H. Cabot's Modern urology, 1918, Vol. III, p. 603, Lea & Febiger, Philadelphia, Pa.
 BRAASCH, W. F. Clinical data on malignant renal tumors. Jour. Amer. Med. Assoc., 1913, lx, 274.
 COLSON, J. A. C. Value of pyelography in the diagnosis of neoplasms of kidney. Jour. Urol., 1921, v, 67.
 GARCEAU, E. Renal, ureteral, perirenal and adrenal tumors, 1909, D. Appleton & Co., New York.
 GLYNN, E. E. The adrenal cortex, its rests and tumors: Its relation to other ductless glands, and especially to sex. Quart. Jour. Med., Oxford, 1911-12, v, 157.
 GRAVES, R. C., AND TEMPLETON, E. R. Combined tumors of the kidney. Jour. Urol., Balto., 1921, v, 517.
 GRAWITZ, P. Die sogenannten Lipome der Niere. Virchow Arch., 1883, xciii, 39.
 HYMAN, A. Tumors of the kidney. Surg., Gyn. & Obstet., 1921, xxxii, 216.
 HINMAN, F. Early diagnosis of renal tumor with the report of five cases and the demonstration of several pyelograms illustrative of the difficulty. Surg., Gyn. & Obstet., 1917, xxiv, 669-680.
 KEYES, E. L., JR. Textbook of urology, 1920, D. Appleton & Co., New York.
 LAWRIE, T. F. Tumors of the kidney: Report of three cases. New York State Med. Jour., 1921, xxi, 279.
 MAC CALLUM, W. G. Textbook of pathology, 1918, W. B. Saunders Co., Philadelphia, Pa.
 MCGOWN, P. E. Papillomatous epithelioma of kidney pelvis. Jour. Amer. Med. Assoc., 1920, lxxv, 1191.
 MILLER, E. M., AND HERBST, R. H. Papillary epithelioma of kidney pelvis. Jour. Amer. Med. Assoc., 1921, lxxvi, 918.
 PERRIN, E., AND AIGROT, G. Epithelioma in kidney pelvis. Jour. Amer. Med. Assoc., 1921, lxxvi, 275.
 PORTER, L., AND CARTER, W. E. Observations on tumors of kidney region in children. Trans. Sec. Dis. Children. A. M. A., 1920, lxxvi, 181.

- RIBBERT, H. Über Bau. Wachsthum und Genese der Angiome, nebst Bemerkungen über Cystenbildung. Virch. Arch., 1898, cli, 381.
- ROLAND, S. Papillary tumor in renal pelvis. Jour. Amer. Med. Assoc., 1920, lxxv, 1752.
- STEVENS, W. E. Tumors of the renal pelvis. Jour. Amer. Med. Assoc., 1920, lxxiv, 1576.
- STOERCK, H. Zur Histogenese der Grawitzischen Nierengeschwiilste. Beitr. z. path. Anat. u. z. allg. Path., Jena, 1908, xliii, 393.
- WILSON, L. B. The embryogenetic relationship of tumors of the kidney, suprarenal and testicle. Ann. Surg., 1913, lvii, 522-534.

SECTION IX

DISEASES OF THE BLOOD

CHAPTER I

PHYSIOLOGY, CYTOLOGY AND PATHOLOGIC PHYSIOLOGY OF THE BLOOD

BY JOHN H. MUSSER, M.D., AND MAXWELL M. WINTROBE, M.D.

- Definition**, p. 739—Importance of the blood in diagnosis, p. 739—Functions of the blood, p. 740—The total quantity of blood, p. 740—Blood volume in health, p. 741—Blood volume in disease, p. 741.
- The erythrocytes and hemoglobin, p. 741—Functions of hemoglobin and red corpuscles, p. 741—The normal erythrocyte, p. 742—Normal number of erythrocytes and quantity of hemoglobin, p. 743—Physiologic variations in number of erythrocytes and quantity of hemoglobin, p. 744—Age, p. 744—Sex, p. 744—Body-build, p. 744—Exercise, p. 744—Diurnal, p. 744—Emotional polycythemia, p. 744—Low barometric pressure, p. 744—"Tropical" anemia, p. 745—The response of the body to demands for hemoglobin and red blood corpuscles, p. 745—Rôle of the spleen, p. 745—The formation of erythrocytes, p. 745—Evidence of increased red cell formation, p. 746—The destruction of erythrocytes, p. 748—Fragmentation and phagocytosis, p. 749—Hemolysis, p. 749—The reticulo-endothelial system, p. 750—Pigment metabolism, p. 750—Evidence of red cell destruction, p. 751—Variation in the size and hemoglobin content of the erythrocyte in disease, p. 752.
- The blood platelets, p. 753—Formation and destruction, p. 753—Functions, p. 754—Coagulation and thrombosis, p. 754.
- The leukocytes, p. 755—Origin and classification, p. 755—The granular leukocytes, p. 756—Myeloblasts, p. 757—Myelocytes, p. 757—Polymorphonuclear cells; neutrophils, eosinophils and basophils, p. 757—The lymphocytes, p. 758—The monocytes, p. 760—Quantitative and qualitative variations in leukocytes in health and disease, p. 760—Biologic properties of leukocytes, p. 760—Passage of leukocytes to the blood stream, p. 760—Removal of leukocytes, p. 761—Normal number of leukocytes, p. 761—Physiologic leukocytosis, p. 761—Leukocytosis, Neutrophilia, p. 761—Functions of the neutrophilic leukocytes, p. 762—Factors associated with neutrophilia, p. 762—Occurrence of neutrophilia, p. 762—The Arneith leukocytic index, p. 763—The Schilling hemogram, p. 763—Leukopenia, p. 765—Eosinophilia, p. 765—Nature and function of eosinophils, p. 765—Occurrence of eosinophilia, p. 765—Basophilic leukocytosis, p. 766—Lymphocytosis, p. 766—Monocytosis, p. 766—The prognostic value of the leukocytic blood picture, p. 767.

Definition.—The blood is so complex and its functions so diverse that to consider all conditions in which abnormal alterations in the blood are found would require the discussion of most of the diseases to which the human body is heir. The present discussion is confined to a consideration of alterations in the quantity or quality, the formation or destruction, of the corpuscular constituents of the blood and a description of the diseases of which the most striking manifestations take the form of alterations in the corpuscular elements of the blood or defects in blood coagulation.

Importance of the Blood in Diagnosis.—The blood is peculiar in that it is a passive carrier which comes in contact with all the tissues. The blood corpuscles are very highly specialized bodies and, in consequence, are particularly susceptible to noxious agents. Again, the hematopoietic organs, the activities of which are readily and clearly manifested in the blood, are promptly influenced by disease noxa. As a result of these special properties, the blood becomes a sensitive reflector of alterations in even the most inaccessible parts of the

body. The importance of numerical and morphologic alterations in the red corpuscles as indications of the severity and a clue to the nature of various diseases, is generally appreciated. The corroborative value of leukocyte counts in cases of septic infection, acute and chronic, is universally known and accepted, be the testimony affirmative or negative, the count itself excessive or significantly low. The diagnostic and prognostic importance of differential leukocyte counts has been particularly emphasized by recent work. These matters will be considered in detail in this chapter. The significance of alterations in the quantity of the normal constituents of blood serum, the diagnostic importance of specific immunity reactions and the value of the isolation of the specific causative organisms of disease which may be found in the blood have already been dealt with in other sections.

Functions of the Blood.—The functions of the blood may be grouped under two main heads, namely, active and passive, the former being concerned with the defense of the body against various toxic agents, while the passive function is concerned with the transportation of various substances associated with the body's metabolism.

In a sense the rôle of the blood in immunity is also passive, the actual weapons of defense being formed in other tissues and organs of the body, notably the hematopoietic system and the liver, while the blood itself serves as the medium for the protective reactions or is merely the transport for the defensive agents. Playing important rôles in the defense of the body against infection are leukocytes, agglutinins, precipitins, hemolysins, antitoxins, amboceptor and complement, alexins, opsonins and the allergic reactions of the body.

The passive function of the blood as the common carrier of the body is most vital to the organism and the life of human tissues is dependent upon oxygen carried to the living cells by the blood stream, the removal of effete waste products, the maintenance of the vital chemical exchanges indispensable to normal functional activity and the supplying of stimuli, chemical and physical, such as are necessary to the normal processes of life. The transportation of the cleavage products of carbohydrates, proteins and fats, of vitamins, inorganic substances and water from the alimentary tract to the liver and other organs, the transmission of glucose to the muscles, the conveyance of waste products such as urea to the kidney, and finally the transportation of enzymes and the secretions of the thyroid, adrenal, pituitary and other endocrine glands from the site of their formation to their point of action, are only a few concrete examples of the importance of the blood as the transport of the body.

The blood plasma itself plays an important rôle in the chemical activities of the tissues. It is maintained in constant acid-base equilibrium, acts as a buffer and participates in the production, distribution and dissipation of heat. The blood corpuscles are associated in an important manner with both the active and the passive functions of the blood, the leukocytes playing an important rôle in immunity while the red corpuscles are specialized instruments, found only in the higher animals, for the transportation of oxygen and, at least indirectly, carbon dioxide. These functions are dealt with in detail under the appropriate headings. Certain constituents of blood plasma, notably fibrinogen, together with the blood platelets are concerned with the processes of repair and the preservation of the blood itself.

The Total Quantity of Blood.—Obvious difficulties arise in the determination of total blood volume. Welker, in 1854, bled animals to death, washed their blood vessels and extracted the hemoglobin still remaining in their tissues. As the result of his experiments he concluded that the total blood mass of mammals constitutes 7.7 per cent of the body weight. This value was later confirmed for human beings by Bischoff who bled two criminals.

Methods of blood volume determination in use at the present time are based on the principle that, by the addition of a definite quantity of a known substance to the circulation, the total quantity of blood may be calculated from the concentration of the foreign substance in a sample of blood. Normal salt solution, tetanus antitoxin, acacia, carbon monoxide and various nontoxic dyes have been used for this purpose. Obvious sources of error arising from the use of such methods are absorption of the foreign substance into the tissues, rapid ex-

cretion or destruction, or failure of this substance to come in contact with all the blood of the body. Again, lymph may be included in the estimated total blood volume. The carbon monoxide method and the Congo red method, or a combination of the two, are now most generally employed. By the former method the saturation of the red cells of an individual to whom a certain amount of carbon monoxide has been administered, is determined and the total quantity of blood is estimated from the relative quantities of erythrocytes and plasma as determined by means of a hematocrit; in the dye method the plasma volume is first determined from the dilution of a given quantity of dye injected into the blood and the total quantity of blood is then estimated from hematocrit values.

BLOOD VOLUME IN HEALTH.—Using the carbon monoxide method values for total blood mass varying from 4.8 per cent to 8.4 per cent of the body weight have been reported, whereas by the dye method higher values (9 per cent) are found. The total blood volume varies with the height, weight, and particularly, according to Rowntree and Brown, the surface area of the body. These workers, using the dye method, found blood volume values ranging from 4000 to 8000 c.c. in normal adults, with an average of 87.7 c.c. for each square meter of body surface. They found slightly higher values in men than in women, and slightly lower values in older as compared with younger adults. In infants the blood volume in relation to body weight is relatively much higher than in adults. High values (100 to 195 c.c. for each kilogram of body weight) are found particularly in the first few weeks of life. Increased quantities of red cells make up the greater proportion of these high values. On the other hand, in relation to surface area infants have relatively less blood than adults. Rapid alterations in blood volume occur in the first few weeks of life, following which more gradual changes take place until values found in adult life are reached.

The total blood volume tends to remain fairly constant despite numerous disturbing influences. The ingestion of large quantities of water and even blood transfusions are associated with only very temporary increases in the total blood volume. The fluid portions of the blood are rapidly removed from the blood vessels by the kidneys and tissues, and even the increase in the cellular elements following transfusion is maintained for only a few days. Likewise reduction in total blood volume as by hemorrhage or excessive vomiting and diarrhea is made up as much as possible by the passage of liquid from the tissues to the blood vessels. The work of Barcroft and his coworkers in England, of Binet and his school in France, and of Izquierdo and Cannon, and Hargis and Mann in this country indicates that the spleen plays an important rôle in buffering mechanically the vascular system against alterations in blood volume.

BLOOD VOLUME IN DISEASE.—Recent work suggests that many formerly maintained conceptions regarding the total quantity of blood in the body in disease must be revised. Most striking is the fact that Rowntree and his associates have found normal or even low blood volume values in hypertension, thus contradicting the doctrine of plethora and negating the indication for venesection in this disease. Likewise, in glomerulonephritis not a "hydremic plethora" but blood volume values below normal have been found. On the other hand, in nephrosis these workers report plasma volume greater than normal. In polycythemia vera and in the leukemias increases in total blood volume have been found, whereas in the anemias a reduction in the volume of blood and cells with a relative and sometimes absolute increase in plasma volume has been noted. In certain diseases associated with splenomegaly, notably cirrhosis of the liver, hemolytic jaundice and Banti's disease, the total blood volume appears to be in excess of normal.

THE ERYTHROCYTES AND HEMOGLOBIN

Functions of Hemoglobin and Red Corpuscles.—The essential chemical nature of life is a process of combustion for which a constant supply of oxygen and a simultaneous removal of carbon dioxide is required. Blood plasma itself is capable of holding only a small quantity of these gases and in the higher animals a more efficient means of gaseous transportation is necessary. This function is chiefly performed by hemoglobin. Hemoglobin itself, however, requires some suitable means of transportation, for in the quantities found in human blood a

simple solution of hemoglobin in plasma would, as Barcroft has pointed out, have physical properties deleterious to the organism. The erythrocyte fulfils this need for a suitable vehicle.

Oxygen is transported as oxyhemoglobin by combination with the hemoglobin molecule. The amount of oxygen which combines with hemoglobin varies with the tension of this gas, more entering into combination at high than at low pressures. This relationship can be expressed as a curve, the oxyhemoglobin dissociation curve (Fig. 1). Between an oxygen tension of one-fifth to one-tenth of an atmosphere, 152 to 76 mm., little change in the oxygen saturation of hemoglobin occurs, but below this point there is an abrupt fall in the oxygen-carrying capacity of hemoglobin. In addition to diminished oxygen tension, the dissociation of oxyhemoglobin is promoted by increased pressure of carbonic and other acids in the tissues, as well as by any local rise of temperature.

The condition in which carbon dioxide is held in the blood is not entirely understood, but it now appears that, in addition to the amount chemically combined with the alkali of the blood as carbonate and that held in physical solu-

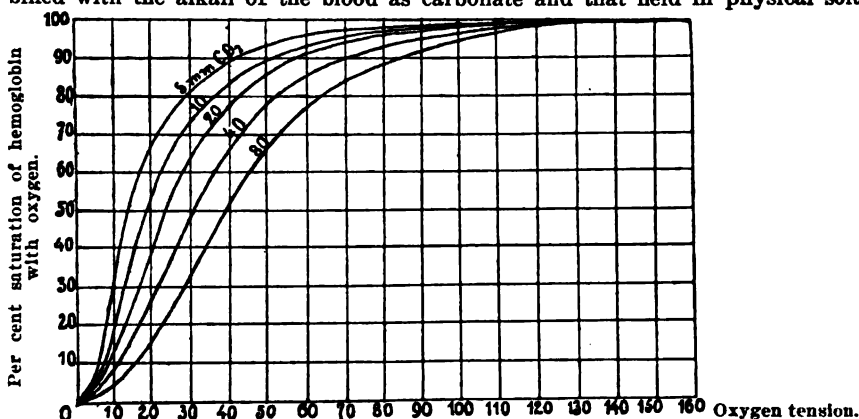


FIG. 1.—OXYHEMOGLOBIN DISSOCIATION CURVE. (Courtesy of W. B. Saunders Co.)

tion in the plasma and corpuscles, an additional large amount is carried in chemical combination with, and is conditioned by, some substance contained in the corpuscles. This substance, it is believed, is hemoglobin which thus indirectly becomes almost as completely responsible for the transport of carbon dioxide as it is for that of oxygen.

In addition to these well known functions of erythrocytes and hemoglobin, the hypothesis has been advanced by Buckman and Darrow that the red cells are important factors in the transmission of water, a theory which is suggested by the occurrence of edema in severe cases of anemia. Robinson has recently added another function, namely, that of an oxidative catalyst which accelerates the oxidation of unsaturated fatty acids. This function is in some way related to the content of iron.

The Normal Erythrocyte.—The normal erythrocyte is a disc which is usually biconcave but may be saucer-shaped. It probably does not possess a histologic cell membrane, but "has on its surface a molecular condensation of lipins which acts as an envelope" (Cooke). Whether the contents of the erythrocyte are fluid or solid in nature is a debated point but most recent evidence favors the former hypothesis. Certain physiologic advantages appear to justify the peculiar biconcave shape of the red corpuscle. Thus, the surface exposed is larger for a given bulk, and besides, the form of red cells is such as to allow the contents to become saturated in all parts of the corpuscle at the same time.

Water (about 61 per cent) and hemoglobin (about 35 per cent) make up the main bulk of the red blood corpuscle. In addition, small quantities of phosphatides, cholesterol, glucose, urea, creatinine, creatine, uric acid, glutathione, thionine, adenine-ribose-nucleotide and various inorganic ions, includ-

ing potassium, chloride, magnesium and phosphate, are found. Of the metals, iron is the well known constituent of hemoglobin. Copper, according to Elvehjem, is present but not in the hemoglobin portion.

The mean diameter of normal red corpuscles is variously stated as being 7.2 to 7.9 μ . An important cause for this variation in reported mean diameter is to be found in differences in technic. It is important to determine the normal for the method one employs. A slight variation in the size of cells is to be found in normal individuals but the range of difference between the largest and smallest cells is probably not more than 3.5 μ . The mean thickness of normal red cells is about 1.6 to 1.8 μ , while the mean corpuscular volume, as calculated from cell counts and hematocrit determinations, is about 85 cubic microns. The extremes of the normal range of mean corpuscular volume are 75 to 95 cubic microns.

The finer structure of the red corpuscle is not completely known. It is frequently spoken of as consisting of stroma and hemoglobin. The average normal red cell contains 28 to 29 micromicrograms* of hemoglobin. "Mean corpuscular hemoglobin," as the content of hemoglobin in the red corpuscle is termed, is calculated from the red cell count and the quantity of hemoglobin in the blood. The extremes of normal range in corpuscular hemoglobin are 26.5 $\gamma\gamma$ to 31.5 $\gamma\gamma$. Approximately 35 per cent of the normal red corpuscle is composed of hemoglobin. "Mean corpuscular hemoglobin concentration" is the term used to express the amount of hemoglobin contained in proportion to the volume of the cell.

The size of the erythrocyte probably varies to a slight extent with the reaction of the blood, red cells becoming somewhat larger as the blood becomes less alkaline in reaction and *vice versa*. The size of the red cell is not at all related to the sex or to the constitutional build of the individual. The cells of infants in their first few weeks of life are distinctly larger than those of adults and contain proportionately more hemoglobin.

The Normal Number of Erythrocytes and Quantity of Hemoglobin.—The average number of red cells in young healthy male adults is 5.5 million per c.mm., rather than the generally stated 5 million, and values ranging from 5 to 6.5 million are to be found in individuals in good health. Any value below 5 million cells may be considered as abnormal. In normal young women the average count is 4.78 million and values between 4.4 and 5.5 million may be considered normal.

On the basis of the best evidence at present available 16.2 gm. per 100 c.c. of blood may be taken as the average quantity of hemoglobin in the blood of a healthy male adult, while the normal range is about 14.5 to 18.5 gm. For women the average is 13.9 gm. with a normal range of 12.5 to 15 gm.

The mean normal volume of packed red cells per 100 c.c. of blood is, for men, 46 c.c. Values between 40 and 50 c.c. may be considered normal. The average for women is 41 c.c., with normal values ranging between 37 and 45 c.c.

The lack of a sufficient number of accurate blood determinations has been the cause of the great differences in the values accepted as the equivalent of 100 per cent of hemoglobin for the various hemoglobinometers. A larger number of accurate blood determinations is now available for the establishment of blood standards. Osgood had pointed out the necessity and greater accuracy of employing as the equivalent of 100 per cent a hemoglobin value which corresponds to 5 million red cells per c.mm., since this is the number of cells considered to be 100 per cent in the calculation of color index. Thus, although the available accurate determinations indicate that 16.2 gm. per 100 c.c. is the average quantity of hemoglobin in the blood of normal young males, this value should not be employed as the equivalent of 100 per cent hemoglobin since the same normal young men have, on the average, 5.5 million red cells per c.mm. Osgood has introduced the term "hemoglobin coefficient" to signify "the number of grams of hemoglobin per cubic centimeter of blood calculated to a red cell count of 5 million per c.mm."

The hemoglobin coefficient derived from accurate blood determinations in a large series of men and women of all ages is 14.5 gm. It is recommended that this value be used as the equivalent of 100 per cent of hemoglobin. For similar reasons the volume coefficient of 42.4 c.c. of packed red cells per 100 c.c. of blood should be used as the equivalent of 100 per cent packed red cells in the calcu-

* A micromicrogram is the millionth of a millilith part of a gram (gram $\times 10^{-12}$) and is abbreviated by the Greek letters *gamma* ($\gamma\gamma$).

lation of the volume index. The nature of the various indices used in the examination of the blood will be discussed in the next chapter.

PHYSIOLOGIC VARIATIONS IN NUMBER OF ERYTHROCYTES AND QUANTITY OF HEMOGLOBIN.—*Age.*—At birth high values for number of red corpuscles (5.5 to 7 million) and for amount of hemoglobin (18 to 23 gm.) are found. The cells are abnormally large and many nucleated and polychromatophilic cells as well as cells varying in size and shape are often observed. These abnormal erythrocytes soon disappear, however, and the values for number of red cells and amount of hemoglobin drop, rapidly at first and then more gradually, to reach a minimum of about 4 or 5 million cells and 12.5 gm. of hemoglobin at 2 years of age, when, it appears from the meager information available, they rise until adult values are reached at about the age of puberty. No differences between the sexes are found until puberty is reached.

No significant differences appear to be associated with old age *per se*. The high values sometimes encountered in apparently healthy elderly individuals are usually associated with some degree of hypertension, emphysema or deficient cardiac power.

Sex.—The well known differences in red cell and hemoglobin values between the two sexes do not become manifest, as has already been mentioned, until puberty. No consistent variation has been proved to occur in association with menstruation. A mild anemia is frequently seen during pregnancy. It may be that this is an effect of the pregnancy *per se*, a manifestation of a condition of hydremia associated with the increased vascular bed, or the result of other causes which will be discussed later.

Body-build.—Individual differences in number of red cells, amount of hemoglobin and volume of packed red cells are associated to a very small extent with individual differences in body-weight, stature, and surface area. These constituents of the blood tend to be slightly greater in heavy and tall individuals, other conditions being equal (Wintrobe).

Exercise.—The work of Broun and others has shown that exercise is followed by a preliminary increase in number of red cells and hemoglobin and a later fall in these constituents. Destruction of erythrocytes begins at the onset of exercise and accounts for the low values found after fatiguing effort but is at first masked by a redistribution or release of corpuscles from some storehouse. Exercise appears to be an important factor in the maintenance of an efficient hematopoietic system. In Broun's experiments animals recently caged did not show as great a decrease in corpuscles as did those confined for several months. Training appears to be associated with a somewhat low threshold of blood cell delivery.

Diurnal.—Diurnal variations in the number of red cells and amount of hemoglobin have been reported by a number of investigators. In many of these studies the limits of error for the technic employed have not been considered. More detailed analyses (see Smith) suggest that under ordinary conditions, either of rest or moderate activity, any fluctuations that occur are within the limit of error of the method. Likewise, relative cell volume appears to remain quite constant. These findings support the view of Rous that under ordinary circumstances there is a delicately balanced coördination between the rates of red cell formation and destruction.

Emotional Polycythemia.—Psychic factors such as excitement and fear are followed by appreciable increases in number of red corpuscles in susceptible individuals. Hematocrit and hemoglobin values do not show as much increase as do the cell counts, indicating thus that the new cells added to the circulation are smaller than the corpuscles already present.

Polycythemia Due to Low Barometric Pressure.—It is now generally agreed that the response to ascent of high altitudes is a rapid increase in the number of erythrocytes and hemoglobin, the degree of the response depending on the rate and height of the ascent as well as on the physical condition of the individual. Following the primary increase there is a more gradual readjustment to the new living conditions which requires several weeks and even months to establish itself. In individuals who live continuously at high altitudes, high values for cells and hemoglobin are constantly found and physical differences, such as in-

crease in the width of the chest in proportion to height and a lessened rib slope, have been noted in natives of these high altitudes (Barcroft).

"Tropical" Anemia.—It has been definitely shown by the reports of a number of investigators that the pallid appearance of so many residents of tropical and subtropical climates is not associated with a "physiological" anemia. The blood of healthy individuals residing in such climates contains as many, or more, red corpuscles with corresponding amounts of hemoglobin as does that of residents of temperate zones (Wintrobe and Miller, Wintrobe).

The Response of the Body to Demands for Hemoglobin and Red Corpuscles.—Under normal conditions a constant moderate activity takes place in the hematopoietic system and the continuous breaking down of erythrocytes from the wear and tear of life is made up by the continuous passage into the circulation of new, normal erythrocytes. To meet increased demands for hemoglobin and red corpuscles there are two mechanisms of red cell delivery.

Rôle of the Spleen.—It has been shown by recent work (Barcroft, Binet and others) that in response to stimuli initiated by circumstances which require an immediate supply of erythrocytes such as exercise, sudden loss of blood and diminished oxygen supply (asphyxia, carbon monoxide poisoning, diminished atmospheric pressure), the spleen contracts and delivers to the circulation red corpuscles which there is every reason to believe are normal and functionally efficient. The spleen is a reservoir for red corpuscles which can be called upon in emergency. The work of Izquierdo and Cannon has shown that the polycythemia arising in response to emotional stimuli, already described, is produced by contractions of the spleen. Barcroft's observations on the living organ have shown that the spleen in life is 2 to 4 times larger than after death and this difference in size is largely made up by the content of red corpuscles. Great alterations in the volume of the spleen normally take place and, when necessary, the spleen may contain as much as one-fifth of the whole blood volume. The contraction of the spleen is, in Barcroft's words, a "kind of fine adjustment" for varying temporary demands. The control of this mechanism appears to be by way of the splanchnic nerves. Adrenalin causes a marked transitory polycythemia. The red cell count may be increased 15 per cent or more by the contraction of the spleen.

In addition to these effects, the same stimuli, if sufficiently great and long continued, as well as other less well understood factors such as those which are the cause of various types of anemia the etiology of which is unknown, arouse an actually increased activity of the hematopoietic system. As a result of this increased activity, immature cells find their way into the blood stream. It is not surprising to discover that these young cells are less efficient than their older fellows. The oxygen consumption of adult erythrocytes is practically nil and they are therefore ideal vehicles for this gas. On the other hand, Harrop has shown that blood which contains abnormal numbers of immature (reticulated) erythrocytes has an oxygen consumption proportional to the percentage of these cells present. Excessive and long continued demands on the hematopoietic system result, therefore, in the passage into general circulation of less efficient red corpuscles.

The Formation of Erythrocytes.—In the embryo the primitive blood cells first appear in "islands" of mesenchyme tissue which, at first distributed throughout the embryo, soon become localized in the liver and later are found in the spleen, lymphatic tissues and finally in the marrow of all the bones. At birth blood formation is centered chiefly in the bone marrow and at a few months of age it becomes entirely confined to this situation. By the age of 16 years blood formation is found to take place only in the vertebrae, sternum, ribs, bones of the skull and pelvis and only to a small extent in the heads of the long bones. Under normal conditions these sites are the only ones in which blood formation occurs, but under appropriate and sufficiently powerful stimulation erythrocytic tissue reappears first in the shafts of the long bones, then in the spleen, and much more rarely in the liver and other parts of the body. Doan points out that in animal experiments the fat filling the entire cavity of a long bone may be replaced within twenty-four hours by a gelatinous matrix in which the generation of blood cells may be observed to have started. Whether this

erythrogenetic tissue is derived from quiescent islands of hemoblastic cells or from primitive reticulo-endothelial tissue is unsettled.

Our knowledge concerning the origin, development and relation of the immature cells seen in the blood during increased blood formation is unfortunately incomplete and evidence is contradictory. Most investigators state that the first cells that are differentiated in the "blood islands" of the yolk sac are hemoglobiniferous elements. Nucleated red corpuscles which differ in size and in the staining qualities of their nuclei (megaloblasts, macroblasts and normoblasts) are later formed. Whether all of these cells are derived from a single primitive stem cell is a debated point. It has not been shown that the size of nucleated red corpuscles nor that of the erythrocytes derived from them is related to their maturity. The manner in which the nucleus of erythroblasts is lost is likewise the subject of debate, some workers holding that the nucleus is dissolved in the cell, whereas others believe that it is extruded from the cell body and is later ingested by phagocytes. Cultures of red bone marrow suggest that erythrocytes are formed by budding from the nuclei of normoblasts (Tower and Herm).

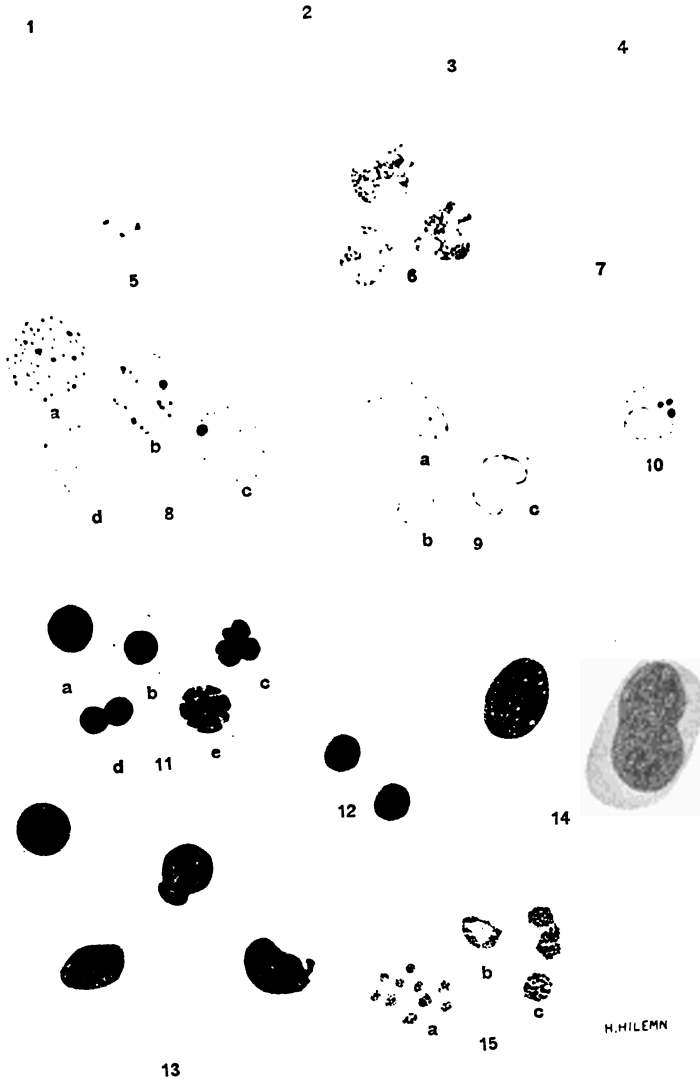
EVIDENCE OF INCREASED RED CELL FORMATION.—Clinical evidence of increased blood formation is slow to appear and not specific in character. Reliance, therefore, must be made on the examination of the circulating blood where the signs of increased activity appear long before there is any manifest improvement in the well-being of the patient. The signs of increased blood formation are here presented more or less in the order of their importance and occurrence.

(1) *Reticulocytes*.—Reticulated red blood cells are probably the surest indication of the state of activity of the hematopoietic system. They cannot be seen in smears stained in the usual manner but require for their demonstration a "vital" staining method by which the living cell and the dye are brought into contact. The technic for staining these cells is, however, so simple that the information which can be gained by a "reticulocyte count" should not be neglected. If fresh blood be allowed to mix with certain dyes (cresyl blue, Janus green) before coagulation or drying has occurred, a limited number of the red cells will show small granules and skein-like filaments. The granules and strands are

PLATE I. NORMAL AND ABNORMAL RED CORPUSCLES AND PLATELETS.
(Wright's stain. 1 mm. = 1 μ .)

- Fig. 1.—Normal red corpuscles (normocytes).
 Fig. 2.—Small red corpuscles (microcytes).
 Fig. 3.—Large red corpuscles (macrocytes).
 Fig. 4.—Exceptionally large red corpuscle (megalocyte) from a case of pernicious anemia.
 Fig. 5.—Abnormally shaped red corpuscles (poikilocytes) from cases of pernicious anemia, chronic posthemorrhagic anemia and sickle cell anemia.
 Fig. 6.—Reticulocytes, stained with cresyl blue, as well as Wright's solution, to show the granulo-reticulo-filamentous network.
 Fig. 7.—Red corpuscles showing polychromatophilia (diffuse basophilia).
 Fig. 8.—Red corpuscles showing basophilic stippling (punctate basophilia); *a*, *b* and *c* are from a case of pernicious anemia, *d* from a case of lead poisoning. The stippling in *d* is much finer than in the other cells; *c* contains a large nuclear fragment; *b* and *d* are diffusely basophilic.
 Fig. 9.—Red corpuscles containing Cabot ring bodies. The cytoplasm of *a* and *c* is diffusely basophilic and contains fine "chromatin dust."
 Fig. 10.—Basophilic red corpuscle containing 3 Howell-Jolly bodies, a Cabot ring body and fine "chromatin dust."
 Fig. 11.—Normoblasts. *c* is the youngest form, the nucleus being composed of coarse strands of chromatin; the nuclei of the other cells are pyknotic; *c* and *d* show karyorrhexis.
 Fig. 12.—Microblasts.
 Fig. 13.—Macroblasts. These differ from normoblasts chiefly in size. The nuclear chromatin is quite coarse.
 Fig. 14.—Megaloblasts. The nuclear chromatin is fine, and there are several nucleoli in each cell. The nuclear membrane is well marked. The cytoplasm is markedly basophilic.
 Fig. 15.—Blood platelets. *a*, normal platelets; *b*, a "giant" platelet from a case of pernicious anemia; *c*, platelets from a case of thrombopenic purpura after splenectomy.

PLATE I



NORMAL AND ABNORMAL RED CORPUSCLES AND PLATELETS.
(Wright's stain. 1 mm. = 1 μ .)

simply mitochondria and are found in all the cells of the human body. When seen in erythrocytes, however, they are an indication of youthfulness and proximity to the nuclear condition. At one time these cells were referred to as skein cells. They were first recognized as indicating youth by Cesaris-Demel and by Meves.

Reticulocytes are found in normal blood, forming about 0.1 to 0.5 per cent (or less) of the erythrocytes. Their presence may be considered to be evidence of normal or physiologic blood regeneration. They are increased in healthy persons during the spring months and values higher than normal are found in the newly-born infant, in pregnancy and in any condition associated with anemia when the bone marrow activity is increased. Increases are found following hemorrhage, in pernicious anemia, in hemolytic jaundice and in chronic leukemia. Very high values are found in familial hemolytic jaundice (15 to 40 per cent) and in sickle-cell anemia. An increase of reticulocytes is the first sign of a remission in pernicious anemia, whether spontaneous or liver-induced. Where erythropoiesis is inadequate, fewer reticulocytes are found than would be expected for the degree of anemia present. In true aplastic anemia they are absent.

(2) *Polychromatophilia*.—When stained with Wright's stain, immature red corpuscles may show a diffuse bluish coloration which is known as "diffuse basophilia" or "polychromatophilia." A limited number of these immature red cells appear in the circulating blood when there is an increased rate of red cell formation. They should be distinguished from the cells seen in poorly stained preparations where all the red cells are bluish.

(3) *Nucleated Erythrocytes*.—Nucleated red corpuscles are never found in the blood stream under normal conditions. Their presence is evidence of pathologically increased rate of growth. It is believed that the passage of erythrocytes into the blood stream is the result of the growth of cells in an inexpandable environment. As the cells mature they are squeezed out toward the marrow capillaries which contain blood flowing at a very slow rate and under low pressure. With increased rate of growth immature forms are forced into the blood. It is obvious that, on the basis of this hypothesis, immature erythrocytes will be found in the blood stream not only when there is increased red cell formation but they may also be forced into the blood stream as the result of the increased growth of other tissues, as occurs when white blood corpuscles are being formed in great excess in leukemia or when bone tumors encroach upon the hematopoietic tissues.

Several types of nucleated red corpuscles are distinguished: (a) Normoblasts, the commonest type of nucleated red corpuscles seen in blood. They are about the same size as the normal red cell or may be a little larger. The "mature" normoblast contains a nucleus which is about half the diameter of the entire cell, is stained a deep, homogeneous purplish-black and shows no trace of internal structure. It is spoken of as being pyknotic. The nucleus may be round, oval or irregularly lobulated. In young forms of the normoblast the cytoplasm is basophilic, the nucleus stains less intensely and shows definite internal structure. Normoblasts give rise to normal erythrocytes.

(b) Macroblasts.—These are nucleated red cells which differ from normoblasts chiefly in size. Their cytoplasm may be basophilic and their nuclei show a definite wheel-spoke arrangement of the chromatin. There is no evidence that the different sizes of erythrocytes are genetically related to one another. The macroblast gives rise to the macrocyte.

(c) Megaloblasts.—Ehrlich and his school described very large nucleated red corpuscles which they considered were pathognomonic of pernicious anemia. These cells are 10 to 20 or more microns in diameter, possess a pink or bluish cytoplasm and contain large nuclei which show a fine chromatin network. The chromatin shows no tendency to a wheel-spoke arrangement. The nucleus may be round, oval or indented. These cells are distinguished from myeloblasts by the presence of a definite nuclear membrane, while the fine chromatin of the nucleus distinguishes them from the lymphoblasts. From both of these early forms of leukocytes differentiation is further aided by the appearance of the cytoplasm. In the megaloblast the latter is frequently slightly acidophilic, particularly near the nucleus, and appears thick at the margins as compared with

that of myeloblasts or lymphoblasts. While Ehrlich's contention is probably incorrect, some pathologists (Piney) still insist that these cells are of different origin and have no relationship to other types of nucleated red corpuscles. Their presence in the blood stream is unquestionably a sign of very florid and abnormal cell formation. On maturation these cells give rise to exceptionally large red corpuscles.

(d) *Microblasts*.—These differ from normoblasts only in that they are smaller than these cells.

(4) *Nuclear Remains*.—Nuclear remains, in the form of fine bluish dots, moderately coarse granules (Howell-Jolly bodies) or bluish thread-like rings and convolutions (Cabot's rings) are frequently seen in red corpuscles in severe anemias. Howell-Jolly bodies are most often encountered in the blood after splenectomy. It is believed that these fragments are remaining portions of incompletely lost nuclei and therefore indicate pathologic erythropoiesis.

In severe anemias, and most characteristically in the blood of individuals suffering from lead poisoning, red cells showing basophilic granules (punctate basophilia, "stippled cells") are found. These granules are not mitochondria, and are distinct from the granules seen in reticulated cells. Whether they are nuclear fragments or cytoplasmic structures is disputed.

(5) *Myeloid Leukocytes*.—Not infrequently during increased erythropoiesis immature leukocytes which are normally found only in the bone marrow may be observed in the blood stream. This "shift to the left" may be the result of the crowding out of the granulocytic elements in the bone marrow by the hyperplastic erythrocytic elements or may be the response on the part of the leukocytes to the same stimulus. On the other hand, leukocytic formation may be depressed in the presence of excessive erythroblastic activity and only very old forms of the granulocytes will in such cases be found in the circulating blood.

(6) *Blood Platelets*.—An increase in the number of blood platelets usually accompanies regenerative activity.

The presence of *anisocytosis*, or variation in the size of the red cells is evidence of disordered and imperfect blood formation. Erythrocytes are distinguished by their size as composing several groups, namely, (1) normocytes, or those of normal size (about 6 to 8.5 μ in diameter); (2) microcytes (smaller than 6 μ); (3) macrocytes (9 to 12.5 μ), and (4) megalocytes which are 13 μ to 20 μ in diameter and are rarely seen in conditions other than pernicious anemia.

The Destruction of Erythrocytes.—It is a biologic truth that with increased specialization of cells their adaptability and durability are more or less proportionately diminished. The unicellular bacterium is, in comparison with the highly specialized cells of the human body, a model of independence and sturdiness. The red corpuscles are examples of division of labor for the sake of maximum efficiency carried to a fine point. They are carriers of oxygen "par excellence" but themselves use practically none. It is not surprising, therefore, to find that, in spite of an environment most suitable for their protection, such highly specialized structures should readily wear out and require constant replacement. The average life of the red corpuscle, estimated from the daily excretion of bile pigments, is given as 10 to 40 days under normal conditions. Under pathologic conditions the life of the corpuscle may be even more brief. Even on the basis of the conservative estimate of 40 days there is, then, a daily loss of at least 60 c.c. of red corpuscles. It is of interest to note that Ashby's observations on the persistence in the circulation of transfused erythrocytes, identified by their specific agglutination group reactions, suggest that such cells remain in the blood thirty days or longer.

The manner in which the destruction of red blood corpuscles takes place is not fully understood. Three possible methods of blood destruction have been suggested, namely, hemolysis, phagocytosis and fragmentation. During pathologic disorders a truly hemolytic process may play an important part, but under normal conditions it is very doubtful if red cells are ever dissolved in the blood plasma. Free hemoglobin is almost never found in normal circulating blood, not even in the blood of the splenic vein. Furthermore, intravascular hemolysis or the injection of whole laked blood is invariably associated with toxic symptoms and rapid excretion of the products of the hemolyzed red cells. The de-

struction of red corpuscles which goes on constantly is unattended by any such phenomena.

Pearce and Austin have pointed out that only two facts in connection with red cell destruction have been established; first, that certain large endothelial cells, located for the most part in the spleen, take up red corpuscles and destroy them; and second, that blood pigment is sometimes present in the Kupffer cells of the liver, indicating thus that they may play a part in blood destruction.

Fragmentation and Phagocytosis.—Rous and Robertson, who have studied this subject thoroughly, feel that phagocytosis will not suffice as a general explanation of normal blood destruction. They searched the body, organ by organ, for disintegrating red corpuscles. Shadows of red cells were not found anywhere, nor were hemolyzing red cells observed. These investigators suggest that the red corpuscles are buffeted in the circulation and gradually subdivide without loss of hemoglobin. Microcytes and poikilocytes are such fragmentation forms. Rous and Robertson have found accumulations of fragmentation forms in the spleen of anemic and plethoric animals and in normal animals the findings have been similar though less striking.

Drinker states that poikilocytes are not found in the bone marrow of "secondary" anemia after the circulating blood has been washed away. The absence of these distorted cells at the site of blood formation suggests that they are truly disintegrating forms. Furthermore, microdissection of red cells shows that they may be torn in pieces without hemoglobin loss. These facts support the contention of Rous and Robertson who conclude that phagocytosis of red corpuscles is slight in man and that normally red cells are "fragmented one by one, while still circulating, to a fine, hemoglobin-containing dust. The cell fragments are rapidly removed from the blood, but their ultimate fate remains to be determined. The facts indicate that they are removed from the blood by the spleen, and under exceptional conditions, by the bone marrow." It is not unlikely that the fine particles are engulfed and dissolved by the phagocytic cells of the reticulo-endothelial system. The high iron content of the spleen at all times, and the increase of iron in this location and in the phagocytic cells of the liver, lymph glands and bone marrow in conditions of increased blood destruction, support such a conception.

Hemolysis.—As has already been mentioned, hemolysis is important as a form of red cell destruction only in pathologic conditions. Hemolytic factors are thought to be important in the pathologic physiology of a number of diseases, but their mode of action is little understood. It is known that many substances may produce solution of the red corpuscles *in vitro*. Thus it is well known that hypotonic solutions will cause swelling and finally bursting of the red corpuscle with liberation of hemoglobin. Again, hypertonic salt solutions, rapid freezing and thawing of red corpuscles or an increase of temperature above 64° C. will produce hemolysis. *In vivo* many factors counteract the influence of physical agents in producing hemolysis. Thus considerable quantities of water must be injected into the blood stream before any appreciable hemolysis can be produced, the cells being protected by the passage of salts from the tissues in the attempt to maintain a uniform osmotic pressure.

Certain physical and chemical agents seem to have a specific hemolytic effect. Thus ammonium salts are themselves hemolytic and act without reference to osmotic pressure. It is possible that sodium citrate may alter corpuscles and render them more susceptible to hemolysis. Because of the presence of lecithin and cholesterol in the stroma of red corpuscles, lipoidal solvents such as ether, chloroform, and bile salts are active hemolytic agents. It does not appear, however, that these substances are associated in any way with the production of disease for during life the proteins and lipoids of blood serum tend to take up such destructive agents. Certain animal and bacterial poisons have hemolytic properties. Snake venoms appear to produce true hemolysis. Again, hemolytic substances have been extracted from many micro-organisms and the blood destruction associated with infections produced by them has been attributed to these substances. Thus, hemolytic substances produced by bacteria during the course of subacute bacterial endocarditis may be responsible for the severe grades of anemia seen in this disease. Finally may be mentioned the produc-

tion of hemolysis as the result of serum action. Serum hemolysis has proved of great importance in medical diagnosis. In blood transfusion hemolysis must be guarded against by the proper selection of donors. In paroxysmal hemoglobinuria there seems to be an autohemolysin in the serum of the patient which is activated by cold.

THE RETICULO-ENDOTHELIAL SYSTEM.—Before proceeding further it is necessary to describe briefly the group of cells to which Aschoff has given the name "reticulo-endothelial system." This system is composed of two varieties of cells, namely, endothelial cells and elongated, irregular cells known as reticulum cells. It appears that these cells are undifferentiated or partly differentiated mesenchymal depots persisting in postnatal life which are capable of further elaboration under suitable circumstances. The possibility of demonstrating the presence of extremely fine intracellular fibrils in the endothelial cells, first demonstrated by Corner, affords, in Piney's opinion, a morphological criterion of the reticulo-endothelium. It should be mentioned, however, that Mallory and Parker have recently disputed Corner's findings.

The cells of the reticulo-endothelial system are widely distributed throughout the body. Forming a part of this system are the *fixed endothelial cells* found lining the blood sinuses of the spleen, the sinuses of lymph nodes, the capillaries of the liver (stellate cells of Kupffer), the bone marrow capillaries and in the adrenal cortex and pituitary. The *reticulum cells* form the connective tissue around blood vessels, and, according to Sabin, the monocytes of the blood are derived from them. The "wandering cells" of tissues, variously known as clasmatocytes, histiocytes, endotheliocytes, splenocytes and macrophages, all of which are more or less identical, are also part of this system and are probably derived from the endothelium.

The functional unity of these widely scattered cells is demonstrated by their extreme avidity for particulate matter. When India ink, carmine particles or colloidal dyes such as pyrrole blue are injected into the blood stream, they are immediately taken up by the cells of the reticulo-endothelial system. Although it is true that almost any type of cell can become phagocytic if suitably and sufficiently stimulated, the reticulo-endothelial cells possess unusual phagocytic properties. Thus, when large quantities of pyrrole blue are injected into the blood stream, these cells become loaded with the colloidal particles of this dye, whereas other cells of the body take up only a few granules. This property has been employed as a test of the functional activity of the reticulo-endothelial system.

The functions of the reticulo-endothelial system are manifold and important. The significance of these cells as the scavengers of the body has long been recognized, but their full rôle in the mechanism of defense is probably not entirely appreciated as yet. Metchnikoff pointed out the importance of these cells in engulfing bacteria and animal parasites. The experiments of Migay and Petroff, as well as those of Kusnetowsky, suggest that these cells play an important part in the formation of hemolysins, precipitins and other antibacterial substances in blood serum. In the form of epithelioid and giant cells (as in the tubercle) they play an important rôle in local defense against acute and chronic infections. Again, reticulo-endothelial tissue is important in the storing of fatty materials such as cholesterol. The feeding of a diet high in cholesterol is followed by an increase of the endothelial cells in the spleen and Eppinger has shown that following splenectomy there is an increase of cholesterol in the blood. Finally, the reticulo-endothelial system plays an important part in blood formation and destruction.

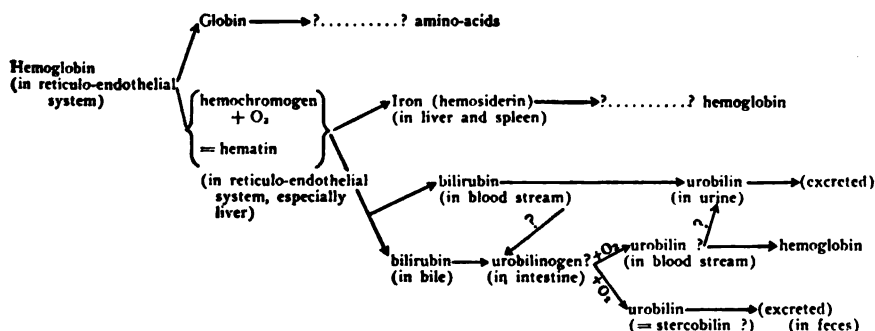
PIGMENT METABOLISM.—Returning now to the consideration of the fate of the red blood corpuscle: it is a recognized fact that the introduction of free hemoglobin into the circulation is followed by an increase in bile pigment in the blood and increased excretion of pigments. Between the broken-down red corpuscle and the pigment end products there is a gap in our knowledge which has not been bridged by information based on conclusive evidence. It is generally believed that hemoglobin is converted into a protein, globin and an iron-containing pigment. The site of this preliminary conversion of hemoglobin is disputed. It is possible that under normal conditions this change takes place in the

liver, but there is no doubt that such changes can take place elsewhere as is shown, for example, by the changing colors of a contused wound. It has been quite conclusively demonstrated by the experiments of Whipple, F. C. Mann and their colleagues that bile pigment can be formed extrahepatically in areas as widely distributed as are the cells of the reticulo-endothelial system which probably are responsible for this conversion. In certain diseases, such as congenital hemolytic jaundice, extrahepatic bile pigment formation is undoubtedly a very important factor.

The fate of hemoglobin is schematically represented in the accompanying diagram. It should be understood that this represents only a working hypothesis based on the best available evidence and is not necessarily a completely true statement of fact. As already mentioned, hemoglobin is probably first converted into globin and an iron-containing pigment. The ultimate fate of globin is not known, but since it is a protein it is probably converted to amino-acids. The iron-containing pigment, which in the reduced form is known as hemochromogen and when oxidized is called hematin, is freed of iron and converted into bilirubin. This change probably takes place chiefly in the liver but may occur also in the spleen, the bone marrow and wherever else reticulo-endothelial tissue is found. The liberated iron is stored chiefly in the liver but also in the spleen and is probably again utilized in the formation of hemoglobin.

Most of the bilirubin thus formed passes into the bile and thence to the in-

Fate of Hemoglobin (Schematic)



testine. Probably a small quantity enters the blood stream. van den Bergh has shown that bile pigment is normally present in the circulating blood in amounts ranging from 0.2 mg. to 1 mg. per 100 c.c. Some of this pigment is oxidized and excreted in the feces as urobilin. Most investigators have stated that another and probably the larger portion of the bile pigment is reabsorbed from the intestine, oxidized to urobilin and either resynthesized to hemoglobin or excreted in the urine. Whipple, however, believes that the bile pigments are waste products and are not reabsorbed, the urobilin of urine being derived from the bilirubin which enters the blood stream directly without preliminary passage through the bowel.

It may be here mentioned that the investigations of van den Bergh suggest that there are two types of bilirubin: (1) bilirubin which is poured into the blood stream by the reticulo-endothelial system, and (2) bilirubin which has passed through the liver cells into the bile. These two types of bilirubin give different reactions to the van den Bergh test.

EVIDENCE OF RED CELL DESTRUCTION.—Clinically *chronic blood destruction* is manifested by few symptoms or signs and none of these are specific in nature. Aside from the general evidence of anemia, moderate degrees of blood destruction cannot be recognized without laboratory assistance. The increased amounts of bile pigments which are formed are excreted rapidly, and unless destruction is quite severe or some degree of biliary obstruction is associated, jaundice does not appear. It should be mentioned, however, that the amount of blood destruction and the degree of jaundice bear no exact relationship and the presence of jaundice is prob-

ably dependent on several other factors such as associated changes in the liver cells and bile capillaries as well as alterations in the viscosity of the bile. From the work of Whipple and Hooper it appears, however, that a purely hematogenous jaundice may occur. Jaundice associated with increased blood destruction never becomes as marked as that due to obstruction of the bile passages and is usually limited to a faint lemon-yellow discoloration of the sclerae or, in the severe cases, at the best to a very slight yellowish tinting of the skin. When blood destruction is long continued the spleen may frequently be palpated. Fever is rare in chronic blood destruction but sometimes some fluctuations of temperature may be noted.

Acute blood destruction, on the other hand, is usually associated with fever and toxic symptoms. Experimental evidence suggests that these effects are caused by the toxic or mechanical action of red cell stromata rather than by the sudden liberation and disintegration of hemoglobin. If the sudden destruction of blood is the result of the injection of incompatible cells by transfusion, alarming respiratory symptoms with cyanosis appear. These may be due to corpuscular agglutination and the production of small pulmonary emboli.

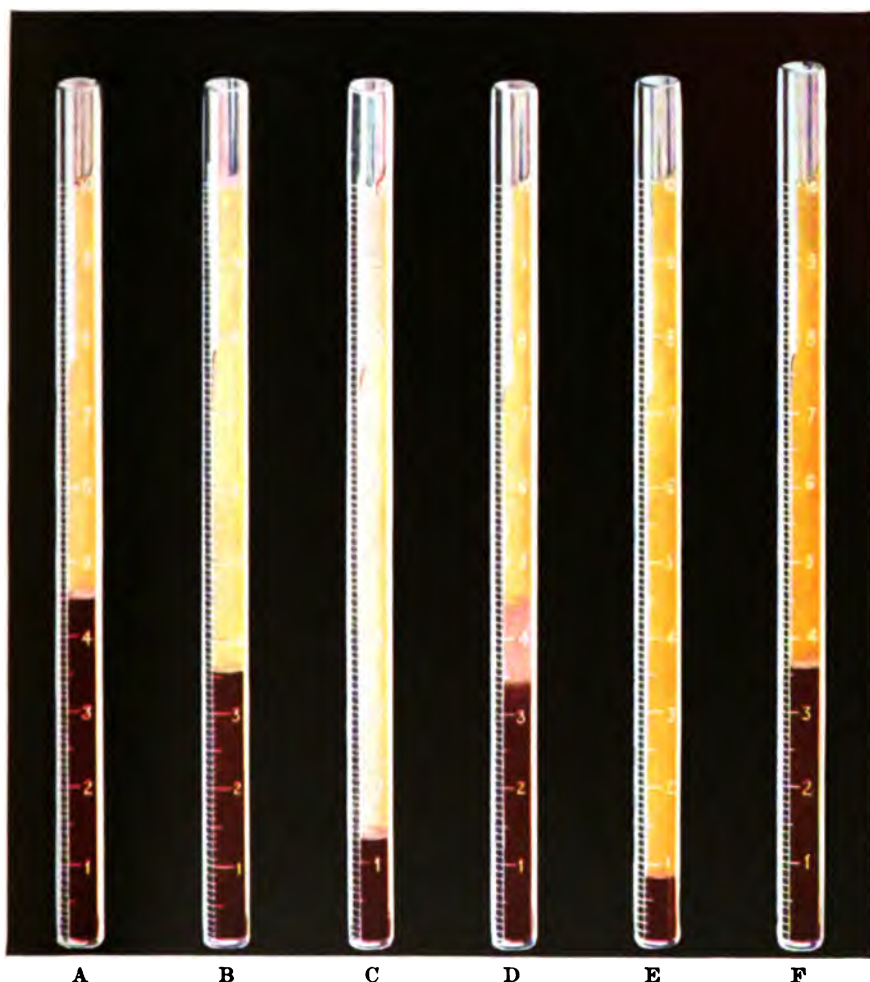
Examination of the blood and excreta yields much valuable evidence of red cell destruction. The extent of reduction in number of red cells and amount of hemoglobin depends, of course, upon the balance between erythrocyte formation and destruction and in itself yields no quantitative information. Blood destruction may be only very slight and yet the number of red cells and amount of hemoglobin may be very low, as in aplastic anemia. Examination of a blood smear will, in the presence of blood destruction, reveal forms which are considered to be produced through destruction of erythrocytes. Most important of these are irregular and particularly small irregular erythrocytes (poikilocytes). Microcytes with regular margins do not necessarily indicate blood destruction. It is probable that they represent one type of abnormal blood formation. Erythrocytic "shadows" and the delicate, almost colorless, veil-like discs, 40 to 50 μ in size, with pink crescents in the margin ("crescent bodies"), sometimes seen in blood smears, probably are the result of red cell destruction (Schilling).

It is by the estimation of the extent of pigment formation that the most satisfactory and valuable evidence of blood destruction is secured. Hemoglobin itself is found in the blood stream and urine only when there is sudden and extensive hemolysis such as occurs in blackwater fever and paroxysmal hemoglobinuria. The failure of hemoglobin to appear in the blood stream except in these circumstances can be explained by the supposition that the process of conversion of erythrocytic "dust" to bilirubin occurs intracellularly. *The presence of bilirubin in blood plasma in abnormal amounts in the absence of biliary obstruction indicates pathologically increased blood destruction* (see Plate II). This may be measured by the icterus index test or by the van den Bergh method (see next chapter). Again, increased blood destruction is followed by *increased excretion of urobilinogen and urobilin in the feces and urobilin in the urine*, and tests for these substances serve as qualitative and quantitative indexes of blood destruction.

Finally, it should be mentioned that increased blood destruction is associated with the deposition of insoluble pigments in various situations, notably in the liver, spleen, bone marrow and kidney. The degree of destruction may, therefore, be determined by appropriate examination of these organs after death.

Variation in the Size and Hemoglobin Content of the Erythrocyte in Disease.—In recent years the work of Price-Jones, who measured the diameters of red cells in various conditions, has attracted the attention of investigators to variations in the size of the erythrocytes in disease. Several methods have been devised for the measurement of red cell diameter and more recently a simple method for calculating the volume, hemoglobin content and hemoglobin "concentration" of erythrocytes has been described (see next chapter). Some general observations arising from these investigations may be mentioned here.

It has been shown that distinct and significant differences in the size and hemoglobin content of erythrocytes are present in various types of anemia and that these differences are, in certain classes of anemia, great enough to be of diagnostic value. On the basis of these differences several types of anemia may be distinguished (Wintrobe):



THE APPEARANCE OF CENTRIFUGALIZED BLOOD IN VARIOUS CONDITIONS.

(Oxalated venous blood was placed in Wintrobe hematocrit tubes and centrifugalized at 3000 revolutions per minute for one-half hour.)

FIG. A.—Normal blood.

FIG. B.—Simple anemia due to chronic infection.

FIG. C.—Chronic posthemorrhagic anemia. The blood plasma is very pale.

FIG. D.—Chronic myeloid leukemia. There is a thick layer of white corpuscles and platelets above the red corpuscles.

FIG. E.—Pernicious anemia. Note the small amount of packed red corpuscles, the very narrow layer of leukocytes and platelets, and the coloring of the blood plasma due to increased bilirubinemia. A smear of this blood is shown in Plate V, Fig. A.

FIG. F.—Catarrhal jaundice and slight simple anemia. In this case the coloring of the blood plasma is due to biliary obstruction rather than to increased blood destruction.

(1) *Macrocytic anemias*.—In this group of conditions, notably represented by pernicious anemia in relapse, the erythrocytes are found on the whole to be distinctly larger than normal. Coincident with this average increase in size is an average increase in the amount of hemoglobin contained in these cells. The increase in size and in hemoglobin content are, however, parallel, so that the normal hemoglobin concentration (relative amount of hemoglobin in the red cells) is maintained. In addition to the marked increase in the mean size of the red corpuscles, there is characteristically a wide and irregular variation in the size of the individual cells.

In sprue a similar macrocytic type of anemia is encountered although frequently the variation in the size of the individual corpuscles is not as great as in pernicious anemia, the increased size of the cells being more uniform and fewer microcytes and poikilocytes being found. Only very rarely is this type of anemia encountered in other diseases (carcinoma of the gastro-intestinal tract, anemia of pregnancy).

(2) *Normocytic anemia*.—In this type of anemia there is a reduction in the number of red cells and in the total amount of hemoglobin but little or no significant alteration in the mean size or hemoglobin content of the cells. Such a blood picture has been noted in aplastic and semi-aplastic forms of anemia as well as immediately following a large hemorrhage.

(3) *Simple microcytic anemia*.—This type of anemia is encountered in the majority of chronic infectious diseases and intoxications and is characterized by a relatively small decrease in the size and hemoglobin content of the erythrocytes and no alteration in the hemoglobin concentration of the cells.

(4) *Hypochromic microcytic anemia*.—This is characterized by a marked reduction in the mean size of the red corpuscles and an even more marked decrease in their hemoglobin content so that in this type of anemia, and apparently in this type of anemia only, values for corpuscular hemoglobin concentration which are distinctly below normal are found. In the anemia resulting from chronic blood loss such marked changes in the size and hemoglobin content of the red corpuscles are encountered. The red cells are very small, values for mean corpuscular volume as low as 55 cubic microns being found. The low values for corpuscular concentration are probably a reflection of the inability of the body to cope with the constant drain on the hemoglobin supply, a defect which is strikingly remedied by the administration of iron.

THE BLOOD PLATELETS (THROMBOCYTES)

The blood platelets are small, irregularly round or oval bodies, generally about 2 to 3 microns in diameter. In blood smears they are frequently found in groups. Their cytoplasm stains faintly blue and contains numerous fine purplish-red granules. No nucleus is present. Under pathologic conditions they may become quite large and may even attain the size of erythrocytes while the granular material may be grouped into conventional nuclear shape. About 200,000 to 300,000 platelets per cubic millimeter are found in normal blood but there is a rather wide fluctuation and normal values differ somewhat with the method of enumeration employed. As a general rule, increased quantities of platelets in the circulating blood are associated with increased bone marrow activity and a diminution in platelets is associated with inactivity. Thus, increases are found in response to hemorrhage and frequently occur in myeloid leukemia and in erythremia (polycythemia vera). A diminution in the number of platelets may be encountered in pernicious anemia, aplastic anemia, acute leukemia and characteristically in certain forms of purpura. They are said to be decreased in anaphylactic shock and in vitamin A deficiency. Experimentally a reduction in the number of blood platelets with hemorrhagic phenomena may be produced by poisoning with large doses of benzol or diphtheria toxin, or by the injection of antiplatelet serum.

Formation and Destruction.—The origin of blood platelets has long been debated. Evidence has been offered to prove their origin from the nuclei of granular leukocytes, or from those of erythroblasts, and it has been maintained by still other investigators that blood platelets are only artifacts resulting from precipitation which may be actually witnessed in shed blood. General opinion now, however, tends to accept the work of J. H. Wright who showed the platelets to be derived from the megakaryocytes of bone marrow. These are giant cells, about 40 microns in diameter, which contain an irregular lobed ring of nuclei. Megakaryocytes may be seen wherever red blood-forming tissue is found and are probably derived from the primitive stem-cell of blood. According to Wright's hypothesis, the pseudopodia of the giant megakaryocytes pass through

the walls of the sinusoids in the bone marrow where portions become constricted off and pass into the circulating blood as platelets. Platelets, therefore, appear to be fragments of cell cytoplasm and are not true cells. It is generally believed that blood platelets remain in the blood stream for only a few days and that the spleen is in some way concerned in their destruction.

Functions.—One of the most important characteristics of blood platelets is their marked tendency to agglutinate and disintegrate. They play an important rôle in protecting the injured epithelium of blood vessels, to which they readily adhere, and similarly collect around cuts, injured surfaces and foreign bodies. When blood is shed the platelets disintegrate and liberate thromboplastin (cephalin) of which they are probably the principal source. Although from this it would appear that they are important in initiating the process of clotting, they do not seem to be quantitatively associated with coagulation, for in hemophilia, where coagulation time is greatly prolonged, platelets are found in normal numbers. On the other hand, in purpura hemorrhagica their number is reduced and bleeding time is greatly prolonged while coagulation time is normal. Their relationship to these diseases will be discussed later.

Coagulation and Thrombosis.—An extravascular blood clot is composed of a meshwork of fibrin threads between which are found red and white blood corpuscles. In the process of coagulation the corpuscles are caught between the fine filaments of fibrin which, therefore, is the final essential substance necessary for blood coagulation. The manner of formation of fibrin is somewhat complex. This subject has been greatly elucidated by the work of Morawitz, Howell and others. According to the latter's theory, the following substances are necessary for the formation of fibrin:

(1) *Fibrinogen*, the immediate precursor of fibrin, a substance found in blood plasma (about 0.4 per cent) and probably formed in the liver.

(2) *Thrombin*, a protein, which is not found in circulating blood but is formed from its inactive precursor, (a) *prothrombin* (thrombogen), which is a globulin or pseudoglobulin normally found in blood plasma. This substance is, according to Howell, derived from platelets which, however, are not its sole source. Prothrombin requires for formation into thrombin, activation by (b) *calcium ions*, derived from the calcium salts in blood plasma.

The initiation of blood clotting appears to be dependent on two substances:

(1) Antiprothrombin (heparin) which is a compound of carbohydrate and glycuronic acid and is probably formed in the liver. It is normally found in the blood and prevents the conversion of prothrombin to thrombin.

(2) Thromboplastin (cephalin) which is a phospholipin derived from tissue extracts or blood platelets.

Any condition which causes the disintegration of blood platelets, such as a moist irregular surface, initiates clotting. As has already been mentioned, the most pronounced characteristic of blood platelets is their tendency to agglutinate and disintegrate. The disintegration of platelets liberates thromboplastin which thereupon unites with antiprothrombin. With the fixation of antiprothrombin, calcium ions are now free to activate prothrombin and permit its transformation to thrombin. The newly formed thrombin unites with fibrinogen to form fibrin. Just what occurs at this stage is not understood, but it is believed that thrombin is absorbed by the fibrinogen particles which then become adhesive and give rise to fine needles and threads of fibrin, an insoluble protein. Fibrin enmeshes the blood corpuscles and later contracts to form a blood clot. These changes may be schematically represented as follows:

From disintegration of blood platelets { Thromboplastin (cephalin)

In blood plasma { Anti-prothrombin
Prothrombin + Ca⁺⁺ = Thrombin + Fibrinogen = Fibrin

Both antiprothrombin and thromboplastin have been isolated by Howell and his coworkers as heparin and cephalin respectively. Heparin is a powerful anti-coagulant prepared most readily from the liver of the dog. Cephalin is recommended as a hemostatic.

The clotting of blood is prevented or impaired by a variety of circumstances. Among these may be mentioned: (a) Removal of fibrin. This can be done only extravascularly. (b) Diminution of fibrinogen. As fibrinogen is formed in the liver, its formation is impaired by any severe destructive changes in this organ as occur, for example, in chloroform or phosphorus poisoning, acute yellow atrophy and yellow fever. In these cases both coagulation and bleeding time are prolonged while blood platelets are not significantly reduced. (c) Diminution or removal of calcium ions. Extravascularly clotting is prevented by the addition of potassium oxalate which precipitates calcium, or sodium citrate which combines with and inactivates the calcium ions. *In vivo* only rarely can delayed coagulation be attributed to a deficiency or inactivity of calcium. Such a condition may occur in certain cases of chronic obstructive jaundice (Lee and Vincent). Administration of large doses of calcium salts is of value in these cases. (d) Deficiency of prothrombin. According to Whipple, this may be the causative factor in melaena neonatorum. Such a theory explains the striking benefits which follow the injection of serum or the transfusion of whole blood in this disease. (e) Excess of antithrombin or antiprothrombin (heparin). The incoagulability of blood produced by hirudin, a substance contained in leech extract, is thought to be due to its ability to prevent the action of thrombin upon fibrinogen. Hence it is spoken of as "antithrombin." It is thought that the impairment of coagulation which follows the intravenous injection of Witte's peptone may be due to excessive production of some antithrombin. Likewise incoagulability of this blood may be due to excessive production of heparin, which, as distinguished from hirudin, prevents the conversion of prothrombin into thrombin and is therefore spoken of as antiprothrombin. (f) Diminution of thromboplastin (cephalin). Such a condition may result from qualitative or quantitative changes in blood platelets, a condition of which we know nothing. It is said that the anticoagulant effect of some snake venoms is due to the destruction or neutralization of cephalin. (g) Deficiency of blood platelets, which in their rôle of initiators of intravascular and extravascular clotting, and as the sources of prothrombin and thromboplastin, are indispensable for the coagulation of blood. (h) Through the use of oiled or paraffined vessels for the collection of blood the blood platelets are prevented from undergoing the rapid change in surface properties that causes them to break down.

Any circumstances which tend to increase the formation of fibrogen, prothrombin or thromboplastin favor the process of coagulation. Stimulation of bone marrow activity with increased production of blood platelets, as occurs following hemorrhage, is one such factor. It has been suggested that dietary factors, such as diets rich in varied proteins and lipins and vitamin A, favor the production of these substances. Conditions which render disintegration of platelets more likely, as moist, rough surfaces, favor coagulation. Such substances as tissue and platelet extracts, cephalin, horse serum and thrombin are useful hemostatics.

Thrombosis.—The process of intravascular coagulation or the formation of thrombi within blood vessels differs somewhat from extravascular coagulation of blood. When endothelium is injured, the platelets adhere in large numbers to the damaged areas and thus form a protective mass which, with the subsequent formation of fibrin, is converted into a solid thrombus. Conditions which favor the formation of thrombi are slowing of the blood stream and abrasions of vessel walls, circumstances which favor the adhesion and disintegration of blood platelets.

THE LEUKOCYTES

Origin and Classification.—Since Hewson discovered the leukocytes and Virchow first recognized their importance in pathologic processes, these cells have been the subject of much intensive study, a study which has been made possible by Ehrlich's introduction of various dyes as a means of investigating the morphology and chemical reactions of the white corpuscles. Although much progress has been made, the origin and relationship of the various types of corpuscles of the blood are still the subject of much controversy and our knowledge is as yet very inadequate. Two schools of thought have arisen concerning the

origin of the blood corpuscles; the one school maintains that all cells of the blood are derived from a single stem cell, while other investigators are of the opinion that there are two or more distinct parent cells. It is not pertinent to the object of this article to discuss the merits of these opinions, but, in recognition of important fundamental contributions to our knowledge at least the names of the "unitarians," Pappenheim, Maximow, Danschakoff and Ferrata, and the "dualists," and polyphyletists, Ehrlich, Naegeli, Schridde, Morawitz and Sabin, should be mentioned.

Ehrlich's sharp division of the blood-forming organs into two groups, the bone marrow and the lymphoid tissues, with a corresponding separation of the leukocytes into granulocytes and non-granulocytes, has been modified and supplemented by more recent work. On embryological as well as on functional grounds the subdivision of all white cells into three classes, the granular leukocytes, the lymphocytes and the monocytes, appears now to be justified.

THE GRANULAR LEUKOCYTES.—The granulocytes are distinguished by the presence in their cytoplasm of a large number of definite and conspicuous granulations. In embryonic life the granulocytes are formed in the liver, spleen and finally in the bone marrow where they are normally exclusively formed in extra-uterine life. Under pathologic conditions they may again arise in the embryonic foci and, in extreme instances of pathologic formation, also in the kidney, skin and lymph glands. The youngest recognizable cell of the granular or "myeloid" series, as this group is termed, is the *myeloblast*. This cell is usually distinctly larger than the adult granulocyte, and possesses a relatively large,

PLATE III. NORMAL AND ABNORMAL WHITE CORPUSCLES.
(Wright's stain. 1 mm. = 1 μ .)

Figs. 1 to 15.—Granulocytes, arranged in order of maturity.

Figs. 1 and 2.—Myeloblasts. The nuclear chromatin is very fine, there is no distinct nuclear membrane, and the nucleus contains five nucleoli. The cytoplasm is deep blue, contains no granules, and there is no perinuclear clear zone.

Figs. 3 and 4.—Myelocytes. The nuclear chromatin is fine. The margin of the nucleus is relatively indistinct and has the appearance of being buried under the granules of the cytoplasm. Two nucleoli are seen in Fig. 3. The cytoplasm is distinctly granular.

Fig. 5.—Metamyelocyte, the "juvenile form" of Schilling. The nucleus is somewhat sausage-shaped and its margins are more distinct than those of the myelocyte.

Fig. 6.—Metamyelocyte or young neutrophil, a later stage than is shown in Fig. 5.

Fig. 7.—Neutrophil with two lobes. The nuclear chromatin is much more coarse in these older cells than in the young granulocytes.

Fig. 8.—A polymorphonuclear neutrophil.

Fig. 9.—Stab-form neutrophil (Schilling). The nucleus is sausage-shaped and stains intensely so that the basi- and oxy-chromatin cannot be distinguished.

Fig. 10.—Giant neutrophil, greatly segmented, from a case of pernicious anemia.

Fig. 11.—Basophil. The granules are characteristically very large and bluish-black in color. The nucleus is not readily distinguished.

Figs. 12 and 13.—Eosinophils. The granules are numerous, large, uniform in size and crimson-red in color.

Fig. 14.—Ruptured neutrophil.

Fig. 15.—Vacuolated neutrophil with pyknotic nucleus.

Fig. 16.—Degenerated nucleus, a so-called "basket-cell."

Figs. 17 to 22.—Cells of the lymphocytic series, 11 to 21, are in order of maturity.

Fig. 17.—Lymphoblast. The nuclear chromatin is coarse in comparison to that of the myeloblast or megaloblast and has a somewhat "stippled" appearance. There are two nucleoli and a distinct nuclear membrane. The cytoplasm is deep blue and shows a pale zone about the nucleus.

Fig. 18.—Young lymphocyte. The nuclear chromatin is dense, but the masses are not as compact as in the older cells. There is a perinuclear clear zone.

Fig. 19.—Young lymphocyte (Rieder cell). The nucleus is lobulated.

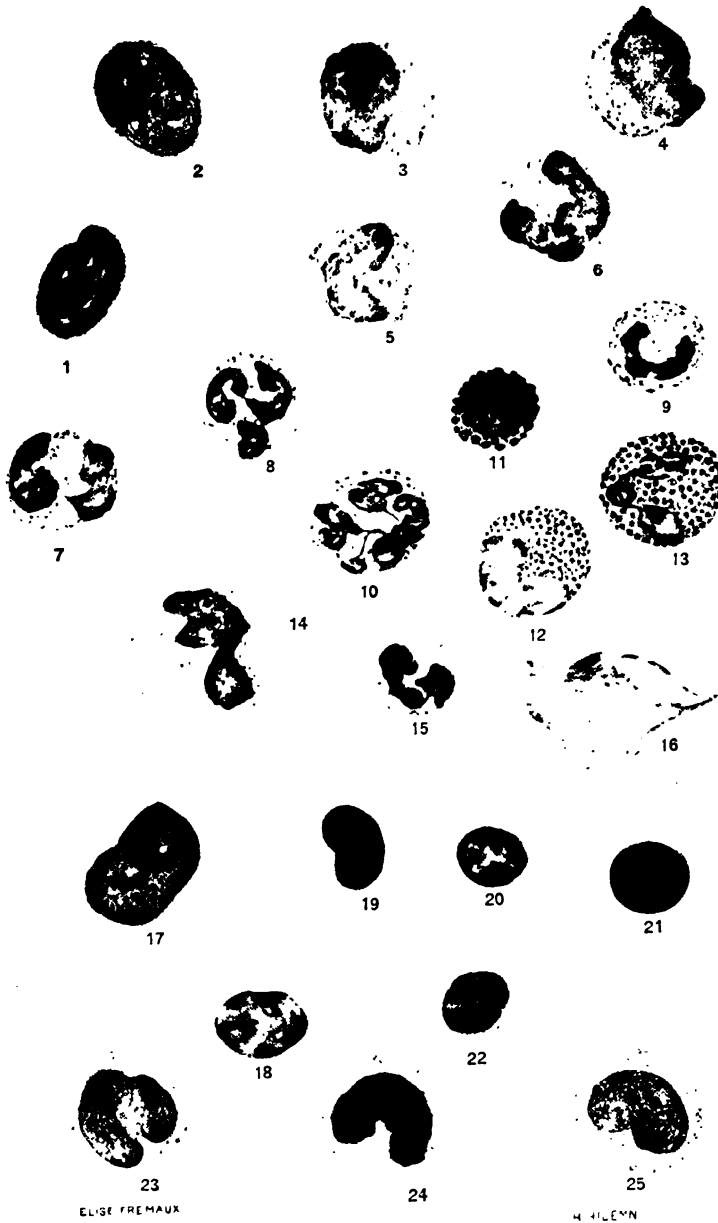
Fig. 20.—Adult lymphocyte. The chromatin is coarse and arranged in wheelspoke fashion.

Fig. 21.—Old lymphocyte. The chromatin masses can scarcely be distinguished.

Fig. 22.—Plasma cell. The nuclear chromatin is arranged in wheelspoke fashion. The cytoplasm is very abundant.

Figs. 23, 24 and 25.—Monocytes. The nuclear chromatin is quite fine and strand-like and thus differs from that of the granulocytes or lymphocytes. The cytoplasm contains many fine, lilac or reddish-blue granules,

PLATE III



NORMAL AND ABNORMAL WHITE CORPUSCLES.
(Wright's stain. 1 mm. = 1 μ .)

often eccentric nucleus which stains a light reddish-purple color. The nucleus is composed of chromatin so fine that an almost homogeneous appearance results. A feature of the nucleus of the myeloblast which distinguishes this cell from the lymphoblast is the fact that the chromatin does not appear to be more dense at the edge of the nucleus, and there is thus no sign of a nuclear membrane. Usually several nucleoli, pale sky-blue in color, are found, and these likewise show no distinct membrane. The nucleus itself is usually round or oval in shape but may occasionally be indented. The cytoplasm of the myeloblast is frequently scanty and stains a deep blue. No perinuclear clear area in the cytoplasm can be distinguished. In the true myeloblast no cytoplasmic granules can be seen.

The recognition of the myeloblast is difficult. It is not readily distinguished from young cells of the lymphocytic or monocytic series and may even be confused with the very primitive red cell, the megaloblast. The nature of the chromatin in the nucleus, whether fine or more coarse, the presence or not of nuclear and nucleolar membranes, as well as the presence of perinuclear clear zones in the cytoplasm, are important points of distinction. (See Table.) In spite of these aids which obviously necessitate the best of staining technic, differentiation is difficult and often conclusions must be presumptive rather than final, the decision depending on the preponderance of older and more easily distinguishable cells of the same series. Thus, in the presence of a large number of young neutrophils and well defined myelocytes, in the absence of more conclusive evidence an unidentified immature cell must be presumed to be a myeloblast, whereas when a large number of nucleated red corpuscles are present and few immature leukocytes are found, a decision in favor of a megaloblast would be presumably correct.

Myelocytes.—The myelocyte is the next distinct stage of maturation in the granular series. The nucleus of the myelocyte presents a slightly more coarse chromatin network than does that of the myeloblast, but like its progenitor, it stains faintly and shows no distinct nuclear membrane. In contrast to the nucleus of the more adult granulocyte or that of the monocyte or lymphocyte, the nucleus of the myelocyte appears to be "buried" under the granules of the cytoplasm. The nucleoli of the myelocyte are smaller than those of the myeloblast and, in fact, may not be visible. The cytoplasm is more pink than blue and characteristically contains granules. As the cell becomes older these granules increase in number and show differences in staining reaction, some being colored lilac or red and others blue-black. A stage in development is finally reached when the granules are either of the neutrophilic, eosinophilic or basophilic variety. The myelocytes containing these granules are spoken of as being neutrophilic, eosinophilic or basophilic and are the immediate precursors of the respective polymorphonuclear leukocytes. The neutrophilic myelocytes are the most numerous cells found in bone marrow.

Once well differentiated granules have appeared in the cytoplasm, the only important alterations which occur during the maturation of a cell of the granular series are to be found in the nucleus itself. First will be noticed an intensification in the staining of the nucleus and a clear distinction between basophilic and oxy-chromatin. Subsequent changes occur in the shape of the nucleus which becomes at first indented and bean-shaped, then sausage-shaped and finally lobed. The nucleoli disappear.

It should be borne in mind that every transition between the typical myeloblast and the myelocyte may be found in the blood and likewise transitions between the myelocyte and more mature cells will be seen. Names are sometimes given to intermediate forms, such as "premyelocyte" for the cell intermediate between the myeloblast and the myelocyte, and "metamyelocyte" (Pappenheim) and "transitional myelocyte" for the cell stage intervening between the myelocyte and the lobulated granulocyte. In his hemogram Schilling classifies as "juvenile forms" the neutrophilic granulocytes the nuclei of which are bean-shaped to sausage-shaped and reticular; that is, not pyknotic.

Polymorphonuclear Neutrophils.—The nucleus takes a deep purplish-blue color, possesses a definite membrane and a deeply staining, rather coarse, chromatin network. It is divided into lobes, two to five or more in number, which are connected with one another by thin strands of chromatin. The number of

lobes is usually considered to be some indication of the age of the cell. The cytoplasm is faint pink and contains fine pink or violet-pink granules.

Polymorphonuclear Eosinophils.—The nuclei of eosinophils are usually larger, paler and less lobulated than those of neutrophils. Eosinophils are distinguished by the presence of large, coarse, highly refractile, red granules which fill the cytoplasm. The large size, uniformity and coarseness of these granules are important differentiating characteristics of eosinophils as compared with neutrophilic granulocytes.

Polymorphonuclear Basophils (Mast Cells).—These cells are distinguished by the presence in their cytoplasm of numerous large, coarse, purplish or bluish-black granules. The nucleus stains even less deeply than does that of the eosinophil and may be partly hidden under the coarse dark granules of the cytoplasm.

THE LYMPHOCYTES.—The lymphocytes in health are formed chiefly in lymphoid tissue such as lymph glands, spleen, thymus, tonsils and Peyer's patches. In such tissue are found germ centers, circumscribed areas in the center of which active formation and division is taking place. Adult lymphocytes are forced by the newly formed, more centrally situated cells to the periphery and the lymph sinuses, whence they reach the blood stream. Very few lymphocytes are seen in the bone marrow in health. Under pathologic conditions, however, they are found in increased numbers even in the bone marrow.

The *lymphocyte* is typically nongranular although occasionally a few reddish-violet (azurophil) cytoplasmic granules may be seen in stained specimens. Lymphocytes may be relatively large (10 to 20 microns in diameter) but are more commonly little larger than red corpuscles. The fully mature lymphocyte consists of a round or slightly indented, eccentric nucleus and a small, crescentic rim of cytoplasm which is sky-blue to deep blue in color. The nucleus stains deep purplish blue and possesses a dense nuclear membrane. The chromatin is very indistinctly differentiated as it consists of very large, deeply-staining masses. Somewhat younger forms are usually larger than the typical adult lymphocyte, but this is not necessarily true, as not infrequently one encounters fully mature lymphocytes which are quite large and possess a relatively large amount of cytoplasm. Young lymphocytes are distinguished by the appearance of the nucleus which stains less intensely than in the fully mature lymphocyte and is composed of less dense masses of chromatin. Clear areas in the nucleus may even be seen and these may be mistaken for nucleoli. Careful examination will in such instances reveal the fact that these spaces do not possess the sharp outlines characteristic of the true nucleoli of lymphoblasts.

Lymphocytes characteristically do not show granulation when stained by the peroxidase method and may in this way be differentiated from granulocytes and monocytes when the diagnosis is otherwise doubtful.

Lymphoblasts.—The very immature cells of the lymphocytic series which are found in the blood only in pathologic conditions, are large cells similar in many ways to myeloblasts and other very immature blood corpuscles. The nucleus of the lymphoblast is large, stains more faintly than that of the mature lymphocyte and possesses a chromatin structure which is finer than that of the mature cell but is more coarse than that of the myeloblast. There is a well defined, fairly dense nuclear membrane. One or two nucleoli with sharp outlines suggesting the presence of nucleolar membranes are present. The cytoplasm stains pale to deep blue and is indistinguishable from that of the myeloblast.

Certain related cells sometimes seen in blood may be described here.

Plasma cells are large cells possessing a rather deep blue cytoplasm which often contains vacuoles. The nucleus is eccentric, round or oval, and contains masses of chromatin which are often arranged in a wheel-spoke fashion. A perinuclear clear area in the cytoplasm is frequently seen. These cells may be confused with erythroblasts. Plasma cells are lymphatic in origin. They are occasionally seen in normal blood, especially when the lymphocytes are increased.

Rieder cells are large lymphocytes with deeply indented or convoluted nuclei.

Türk's irritation forms are large cells with intensely blue cytoplasm which may be vacuolated but contains no granules. The nucleus is eccentric, large, round and darkly staining. These cells are thought to be pathologic forms re-

MORPHOLOGIC CHARACTERISTICS OF THE LEUKOCYTES (WRIGHT'S STAIN)

Name of Cell	Size	Nucleus					Cytoplasm				
		Position	Shape	Color	Chromatin	Nuclear Membrane	Nucleoli	Relative Amount	Color	Peri-nuclear clear zone	Granules
1. <i>Granulocytes</i> (a) Myeloblast	15-20 μ	eccentric	round or oval	light reddish purple	very fine	none	4-5	scanty	deep blue	none	none
(b) Myelocyte	12-18 μ	central or eccentric	oval or slightly indented	reddish purple	fine	none	smaller, fewer	moderate	bluish pink	none	red or blue-black, fine or coarse
(c) Metamyelocyte ("Juvenile" form)	10-18 μ	central	horse-shoe or sausage	light purplish blue	basal- and oxy-chromatin clearly distinguished	present	none	plentiful	pink	none	neutrophilic, eosinophilic or basophilic
(d) "Stab-form" (Schilling)	10-15 μ	central	horse-shoe or sausage	blue-black	structureless, "pyknotic"	present	none	plentiful	pink	none	stained poorly or too deeply
(e) Polymorphonuclear neutrophil	10-15 μ	central	2-5 or more lobes	deep purplish blue	rather coarse	present	none	plentiful	faint pink	none	fine pink or violet-pink
(f) Polymorphonuclear eosinophil	10-15 μ	central	2-3 lobes	pale purplish blue	coarse	present	none	plentiful	bluish pink	none	large, coarse, uniform in size, crimson-red, numerous
(g) Polymorphonuclear basophil	10-15 μ	central	2-3 lobes	pale purplish blue	coarse, overlaid with granules	present	none	plentiful	faint pink	none	large, coarse, uniform, bluish-black
2. <i>Lymphocytes</i> (a) Lymphoblast	15-20 μ	eccentric	round or oval	light reddish purple	moderately coarse particles, "stippled"	fairly dense	1-2	scanty	deep blue	present	none
(b) Young lymphocyte	9-18 μ	eccentric	round or oval	light purplish blue	distinct particles and masses	fairly dense	none	plentiful usually	sky-blue to deep blue	present	none or few "saurophilic"
(c) Adult lymphocyte	7-10 μ and larger (12-15 μ)	eccentric	round or slightly indented	deep purplish blue	indistinct large masses	dense	none	scanty usually	sky-blue to deep blue	present	none or very few "saurophilic"
Plasma cells	12-20 μ	eccentric	round or oval	light purplish blue	wheel-spoke	fairly dense	1-2 or none	plentiful	rather deep blue	present	none
3. <i>Monocyte</i>	12-20 μ	eccentric	round, oval, notched, or horse-shoe	pale bluish violet	fine reticulated skein-like	present	none	abundant	grayish or cloudy blue	none	abundant, fine, lilac or reddish blue

lated to lymphoblasts or plasma cells and are found in instances of intense leukopoietic stimulation.

THE MONOCYTES.—The monocytes, according to Sabin, are a strain of cells separate and distinct from the granulocytes or the lymphocytes. In her opinion they are formed from the reticulum cells of bone marrow and other organs and are related to the erythrocytes, as well as to the clasmatocytes of the connective tissues. Other hematologists, as Naegeli and Piney, consider that the monocyte is a derivative of the reticulo-endothelial tissue only by the intermediation of the myeloblast and "is as much a myeloid cell as is any other granular leukocyte."

The monocyte is the largest cell of the blood. The cytoplasm is abundant, grayish or cloudy blue in color, and contains abundant fine lilac or reddish-blue granules which have the appearance of fine dust. In overstained preparations these granules may appear coarse and cause confusion with granulocytes. The granules usually give the oxydase reaction. There is no perinuclear clear zone in the cytoplasm as is seen in lymphocytes. The nucleus is large, eccentric and round, oval, notched, or even horse-shoe or convoluted in shape. Monocytes showing horse-shoe or even lobed nuclei were spoken of as "transitional" cells by Ehrlich on the mistaken supposition that they represented a stage in the development of the neutrophilic leukocytes. The nucleus of the monocyte is pale bluish-violet in color and, in contrast to that of the lymphocyte, appears thin. The chromatin is fine and reticulated and, by contrast to the coarse strands of the granulocytes and the dense masses of the lymphocytes, serves to differentiate these cells. Lymphocytes should be distinguished on the basis of these structural differences rather than on the basis of size.

Pathologic Leukocytes.—All the cells described, except perhaps Türk's irritation forms, are leukocytes which are normally found in the body although not all of them are normally found in the circulating blood. However, changes may take place in any of these cells as the result of the action of toxic agents. One such degenerative form is the "*stab*" or "*staff*" *neutrophil* of Schilling. This is a neutrophil matured without segmentation of the nucleus. The nucleus is sausage-shaped, narrow and structureless and stains deeply and uniformly (pyknotic). The granules may be too highly stained or too little. Similar changes are likewise an indication of toxic degeneration or impaired development in other leukocytes, as are also vacuolization of the cytoplasm or nucleus, abnormal staining of the cytoplasm and, in good preparations, a tendency to smudging and ready fragility of the cells.

Quantitative and Qualitative Variations in Leukocytes in Health and Disease.

BIOLOGIC PROPERTIES OF LEUKOCYTES.—Quantitative and qualitative alterations in the leukocytes found in the blood current are dependent on the fundamental biologic properties of the white corpuscles. The white blood corpuscles all possess ameboid motion in varying degrees. The direction in which they move is thought to be determined by chemical substances emanating from foreign particles, a property which is spoken of as *chemotaxis*. Usually bacteria and foreign substances exert an attractive influence (positive chemotaxis). As a result these foreign bodies become surrounded by leukocytes and usually there also occurs an increase in the number of leukocytes in the blood stream. The chemotaxis is frequently specific. That is, the foreign substance usually attracts and often stimulates the production and liberation into the blood stream of one type of white corpuscle. On the other hand, in overwhelming infections and in certain types of infection this positive chemotactic influence may be absent or there may even perhaps be a negative chemotactic effect. Conditions such as typhoid fever or uncomplicated tuberculosis attract leukocytes to the site of activity without at the same time bringing about an increase in the number of these cells in the blood stream. On all of these phenomena the diagnostic value of total and differential leukocyte counts depends.

Phagocytosis, the engulfing of foreign particles, is the chief function of the white corpuscles. Closely associated with this rôle is the presence in these cells of various *ferments*, oxidizing, proteolytic and, in the case of lymphocytes, fat-splitting in nature, which bring about the solution or digestion of the foreign body.

PASSAGE OF LEUKOCYTES INTO THE BLOOD STREAM.—The white corpuscles normally seen in the blood stream are all fully developed and mature. In the

case of the neutrophils and perhaps also the monocytes, the entrance of these cells into the blood is under normal conditions probably largely dependent on their power of locomotion. Bone marrow is pierced by a network of sinuses lined by endothelium and about three times the width of blood capillaries. It is believed that mature granulocytes pass between the endothelial cells into these sinuses. As has already been mentioned, lymphocytes probably are mainly forced into the blood stream as the result of "growth pressure."

Alterations in the number of leukocytes in the peripheral blood are first the result of a redistribution of cells in the tissues and a draining of the available supply in the "reservoirs," the bone marrow and the lymphatic tissues. Greater demands than can be met by such a response call forth increased formation of the specific cells required. When the stimulus is sufficiently great, immature forms are forced into the blood, probably chiefly as the result of increased growth pressure within a relatively inexpandable medium. The immature cells are less actively ameboid than adult types and probably therefore less efficient. The presence of immature forms in the peripheral blood, then, is evidence of response beyond the point of maximum efficiency. In spite of the absence of any very large "reservoir," the response to demands for more cells is, in the case of neutrophils, very rapid.

REMOVAL OF LEUKOCYTES.—The exact fate of the leukocytes is not definitely known. They remain in the blood stream under normal conditions for a few days at the most and are probably removed as cellular detritus by the reticulo-endothelial system. Bunting and Huston have shown that lymphocytes pass onto the surfaces of mucous membranes, especially those of the gastro-intestinal tract, and pass off with the excreta of the body.

NORMAL NUMBER OF LEUKOCYTES.—There is a normal wide fluctuation in the number of leukocytes in the peripheral blood. The average normal value may be considered as being 7,000 per c.mm. and varies between 5,000 and 10,000. An increase in the total count above 10,000 is arbitrarily designated *leukocytosis*, while a reduction below 5,000 constitutes *leukopenia*.

PHYSIOLOGIC LEUKOCYTOSIS.—Although strictly speaking all increases in the number of leukocytes are physiologic in the sense that they manifest the response of the body to increased demands, the term physiologic leukocytosis is restricted to those fluctuations found in healthy individuals.

The diurnal fluctuations in the leukocyte count are so extensive under normal conditions and so dependent on a variety of factors that the leukocytosis which has been so frequently described as accompanying normal digestion must be questioned. Garrey and Butler have found that under conditions of complete mental and physical relaxation the leukocyte count is reduced to a minimum of about 5,000 to 6,000 cells. This basal count is constant in a given individual from day to day. Fluctuations in the leukocyte count are evidence of physical or mental unrest or activity. These workers have found that there is no true *digestive* leukocytosis although fluids introduced into the stomach do affect the count. *Exercise* is associated with an increase, particularly of neutrophils. As many as 35,000 cells were found following very severe exertion. *Nervous and psychic factors* are important. Garrey and Butler feel that physiologic leukocytosis is a result of vascular readjustment.

In the *newly-born infant* values as high as 12,000 to 20,000 and even 35,000 leukocytes may be found. The proportion of neutrophils may be greatly increased. The total count begins to fall gradually after 2 to 4 days but remains at 10,000 to 15,000 during the first year of life. Following the preliminary increase in the number of neutrophils, there is a gradual increase in the relative number of lymphocytes which soon constitute as much as 40 to 60 per cent of all the white cells present. Adult values for the total and differential count are not reached before two to five years of age.

During the late stages of *pregnancy*, and for about a week following delivery, a moderate leukocytosis of the neutrophilic type, amounting to 13,000 and even 16,000 white cells, is the rule. This probably signifies the constant existence in the blood of the mother of small amounts of protein material foreign to her.

LEUKOCYTOSIS—NEUTROPHILIA.—Although strictly speaking leukocytosis means any increase in the number of white corpuscles, the term usually refers

to increases in which the neutrophilic leukocytes play the major part. To such increases the term "neutrophilia" may be applied. Neutrophilia may take the form of an absolute increase in the number of neutrophils or may refer only to a relative increase in the proportion of these cells, which normally make up 60 to 67 per cent of the white corpuscles or, in absolute numbers, 3,000 to 6,500 per c.mm.

Functions of the Neutrophilic Leukocytes.—When fresh blood is stained and examined by "vital" methods, the neutrophils are seen to be very actively amoeboid, stopping, as Sabin says, only to change their direction. They can squeeze through the minute interstices between endothelial cells and wander in the spaces of the connective tissues. As already mentioned, they possess a high degree of chemotaxis and not only engulf foreign bodies such as bacteria but also digest them. This property of digestion is dependent on the presence of oxidative and proteolytic ferments. Since they engulf only minute foreign bodies they are spoken of as "microphages."

Factors Associated with Neutrophilia.—Whether neutrophilia will develop in a given case depends on several factors:

(1) The Type of Invading Organism. Pyogenic, and particularly coccal, bacteria call forth a neutrophilic response when they invade the body tissue, whereas other bacteria, such as typhoid, paratyphoid and tubercle bacilli, have no such effect.

(2) The Localization of the Process. A generalized infection, even when it is the result of an invasion of cocci, as in streptococcal septicemia, is not associated with neutrophilia, whereas a more localized process tends to stimulate neutrophil formation even though the invading organism is one which usually is associated with leukopenia. The neutrophilia seen in tuberculous meningitis is an example of such a response.

(3) The virulence of the invading organism, the reaction of the patient and his general resistance are likewise important factors. Thus, when otherwise expected, neutrophilia will be absent when the infection is very mild, when the infection is overwhelming, or when the person involved is too much enfeebled and nonresistant. The leukopenia of acute fulminating suppurative appendicitis is an important illustration.

Occurrence of Neutrophilia.—Neutrophilia is found in:

(1) Acute infections with or without suppuration. In conditions such as wound infections, acute abdominal inflammation, tonsillitis, acute rheumatic fever, infections caused by streptococci, staphylococci, pneumococci, meningococci, catarrhal micrococci, and colon and diphtheria bacilli, values for total white cells ranging from 12,000 to 20,000 per c.mm. are found. Pneumococcal pneumonia characteristically calls forth a very active response and values as high as 30,000 and 40,000 are common. In all these infections, depending on a variety of factors already mentioned, values as high as 50,000 and even 100,000 may occasionally be encountered.

(2) Intoxications. In uremia, illuminating gas poisoning, lead poisoning, the acute stages of gout and sometimes in poisoning from turpentine, acetanilid, potassium chlorate, digitalis and arsphenamine, leukocytosis occurs. In lead colic values as high as 20,000 may be found. Following the injection of foreign protein there is a preliminary leukopenia which is soon followed by leukocytosis.

(3) Following acute hemorrhage neutrophilia occurs. This may be the effect on the hemopoietic organs of loss of blood *per se*, or may be partially dependent on the rapid flow of tissue juice and, with it, large quantities of protein into the blood stream. It should be borne in mind that a ruptured ectopic gestation may call forth as great a leukocytosis as acute appendicitis or peritonitis.

(4) Postoperatively, for 12 to 36 hours a leukocytosis occurs, probably as the result of the extensive tissue injury and liberation of protein.

(5) In rapidly forming malignant growths, especially those involving the liver, gastro-intestinal tract and bone marrow.

(6) In myeloid leukemia.

So far the discussion of neutrophilia has been confined chiefly to quantitative variations. As a general rule the total numerical increase of leukocytes in a given case may be regarded as measuring the resistance of the individual attacked. The percentage increase of neutrophils and the qualitative changes in

these cells are, however, of great importance in measuring the degree of toxemia and, as Arneth and later Schilling have stressed, are very important indications of prognosis. Furthermore, in such instances in which the leukocyte count is normal, as when the infection is subacute or chronic in type, or, on the other hand, when the infection is very severe and the patient's resistance is poor, it is only from the observation of qualitative changes in the leukocytes that any information can be derived by the examination of the blood cells.

The Arneth Leukocytic Index.—In an attempt to make use of the observations that an excessive demand calls forth a supply of younger neutrophils and that the severity of the infection may to some extent be gauged by the nature of this response, Arneth has studied the granulocytes in great detail. He has subdivided these cells according to the shape of their nuclei into five classes and a number of subclasses which make up a total of some eighty types of cells. In the first class he includes the myelocytes and metamyelocytes, the so-called M, W and T cells. In the second and succeeding classes are included different forms of two-lobed, three-lobed, four-lobed and finally five- or more-lobed neutrophils respectively. One hundred neutrophils are examined and tabulated according to each of these subdivisions. The classification rests on the presumption that the age of a neutrophilic leukocyte is indicated by the number of lobes in its nucleus, age and lobulation varying directly with one another. As the tabulations are written from left to right across a page with the first class at the extreme left, the term "shift to the left" was introduced by Arneth to designate an increase in the number of younger cells (first and second class) while a "shift to the right" indicated a preponderance of multilobed cells.

Arneth's technic has not received widespread approval. His method of determining the age of neutrophils has met objections on theoretical grounds and Naegeli has pointed out that toxic influences may interrupt the maturation of cells and cause such changes in their structure as to prevent any accurate estimation of their age by Arneth's method. In addition to these theoretical objections, the technical difficulties of so extensive a classification make the method impractical.

The Schilling Hemogram.—Schilling has made certain modifications in the Arneth leukocytic index which counter these theoretical objections and render the method quite practical. A differential leukocytic count is made in the usual manner except that the neutrophils are subdivided into four classes instead of the customary one or two. The hemogram (Fig. 2) consists of the following classes of cells:

		Per Cent	
Basophils	Normally 0.5	(0-1)
Eosinophils	" 3	(2-4)
	Myelocytes (round or oval nuclei)	" 0	
	Metamyelocytes or Juveniles (indented, sausage-shaped or S-shaped nucleus, basophilic and oxy-chromatin clearly differentiated)	" 0	(0-1)
Neutrophils	Staff forms, "Stabkernige" (nucleus ribbon-like and twisted or sausage-shaped but pyknotic)	" 4	(3-5)
	Segmented	" 63	(58-66)
Lymphocytes	" 23	(21-25)
Large mononuclears or monocytes	" 6	(4-8)

Schilling's grouping of the neutrophils in order of maturity as myelocytes, metamyelocytes and segmented forms is unquestioned. His hemogram has the further advantage that the pathologic forms of neutrophils the normal maturation of which has been inhibited by noxious influences, the *Stabkernige* or staff forms, are distinguished and recorded. By this hemogram Arneth's shift to the left, or "regenerative shift" as Schilling prefers to call it, may still be recognized and this is done with much less technical difficulty. It has the same significance as in the Arneth index, namely, the greater the shift to the left the more intense and severe the stimulus, be it unusually severe exercise or a very serious infection. Neutrophilia without shift is an accompaniment of mild exercise or other mild types of physiologic leukocytosis. Neutrophilia with simple or "hyporegenerative shift" (over 5 per cent of staff forms) is found in instances of mild infection, very

		Clinical Diagnosis..... Appendicitis..... Date 2/26/19.....											Out of 200	%	Normal %
B. Basophiles													1	0.5	0.5 (0-1)
E. Eosinophiles													3	1.5	3 (0-6)
M. Myelocytes													0	0	0
J. Young forms (Metamyelocytes)													8	4	0 (1)
St. Stab forms													52	26	4 (0-6)
S. Segmented nucleus													104	52	63 (50-80) N. Seg.
L. Lymphocytes													18	9	23 (10-35) Lymphocytes
Gr.M. Large mononuclear and forms													14	7	6 (0-10) L. Mon.
Differential Counting Table for Leukocytes by Dr. V. Schilling		SPECIAL REMARKS:											Erythrocytes total count (normal 3-4½ millions) 4,500,000		
		Leukocytes total count 17,000 (normal 6-8000) Plasma cells — Irritation forms: 7 Atypical: 7 promyelocyte with leucoplakic granules Summary of blood findings: hyperleukocytosis, hypermyelocytosis, neutrophilia with regenerative shift, lymphocytosis — very slight anemia, probable appendicitis											Hemoglobin: 25 Polychromasia + Normoblasts — Anisocytosis — Special forms and parasites: none Index 85/90 = 0.94 Basophilic stippling — Megakaryoblasts — Polikilocytes — Blood platelets: numerous		

FIG. 2.—SCHILLING CHART FOR DIFFERENTIAL LEUKOCYTE COUNT. (Schilling and Gradwohl, The Blood Picture, C. V. Mosby Co.)

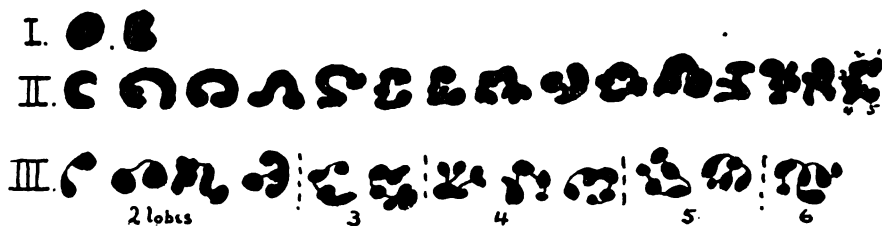


FIG. 3.—VARIOUS FORMS OF THE NEUTROPHIL NUCLEUS, AS SEEN IN STAINED SPREADS: I, MYELOCYTES AND METAMYELOCYTES; II, UNSEGMENTED (YOUNG) FORMS. THE FIVE LOBULATIONS OF THE LAST NUCLEUS IN THE SECOND ROW ARE NUMBERED TO SHOW THE POSSIBLE CONFUSION WITH SEGMENTED FORMS. THIS IS CONSIDERED AN UNSEGMENTED FORM ON ACCOUNT OF THE THICK CONNECTING BANDS. III, SEGMENTED (OLD) FORMS WITH 2 TO 6 LOBES. (Pons and Krumbhaar, J. Lab. and Clin. Med.)

good resistance or favorable localization of the infective process. The hyporegenerative shift is seen in such conditions as superficial benign or encapsulated septic processes, slight catarrhal appendicitis and very chronic diseases.

In addition to the Schilling hemogram here described, there have been proposed numerous other modifications of the Arneht method of classifying granulocytes. Among these may be mentioned the modifications of Cooke and Ponder and of Pons and Krumbhaar. The latter point out that the essential clinical purpose is served if, in the course of the customary leukocyte differential count, the neutrophils are subdivided into 3 groups (Fig. 3), namely: (1) myelocytes and metamyelocytes with round or slightly indented nuclei; (2) nonsegmented (young) forms, in which the nuclear material is connected by broad bands, and (3) segmented (old) forms, in which two or more groups of nuclear material are joined by narrow filaments. Myelocytes and metamyelocytes never occur normally in blood. Nonsegmented forms make up about 3 to 6 per cent and at most 10 per cent of the leukocytes seen under normal conditions, while the segmented forms account for from 55 to 65 per cent of the cells.

LEUKOPENIA.—As a rule in leukopenia the diminution affects chiefly the granulocytes so that there is a relative lymphocytosis. Such a blood picture may be encountered in:

1. Infections caused by certain organisms, such as those producing typhoid fever, paratyphoid fever, tuberculosis, influenza, measles, malaria, undulant fever, leprosy and trypanosomiasis.

2. Overwhelming infections due to any type of organism. A striking example is found in the syndrome described by Schultze, "agranulocytic angina."

3. Exhaustion of the bone marrow as in aplastic anemia; or crowding out of the leukopoietic tissues by excessive and abnormal erythropoiesis as in pernicious anemia.

4. Cachectic and debilitated states.

5. Intoxications and chronic poisoning by benzol, lead or mercury.

6. Collection of leukocytes in internal organs as in anaphylactic shock.

Rarely in leukopenia the decrease affects chiefly the lymphocytes. This may be seen in instances of excessive exposure to roentgen rays or radium.

EOSINOPHILIA.—By eosinophilia is meant an increase in the number of eosinophilic granulocytes beyond the normal limit which may be taken as about 250 eosinophils per cubic millimeter or about 3 per cent of the normal white cell count.

The *nature* and *functions* of the eosinophils still remain a subject concerning which we know very little. It has been suggested that these cells are transformations of neutrophils or lymphocytes and that the conspicuous granules are hemoglobin or other foreign particles ingested by these cells. Since Opie showed that the bone marrow of animals with eosinophilia is rich in eosinophils, the opinion that they are specifically differentiated cells has met with more general acceptance. Eosinophils are much less actively ameboid than neutrophils and their chief function probably consists in bringing about the disintegration and removal of foreign protein from the tissues.

Eosinophilia is met with in:

1. Infestation with worms and other parasites such as hookworm, *Taenia saginata*, *Trichocephalus*, *Hymenolepis nana*, *Diphyllobothrium latum*, *Echinococcus* and, less frequently, *Ascaris* and *Oxyuris*. In trichiniasis eosinophilia is unusually marked, total eosinophil counts even as great as 15,000 being found. Eosinophilia is rare in amebic dysentery.

2. Allergic phenomena; serum disease, bronchial asthma, urticaria and angio-neurotic edema.

3. Skin diseases. The degree of eosinophilia in such conditions appears to depend to a large extent on the amount of skin involved.

4. During convalescence from an infection.

5. Eosinophilia may occasionally be seen in a large variety of conditions among which may be mentioned Hodgkin's disease (as great as 60 per cent), certain tumors of the ovary, and carcinoma, especially when there are serous metastases. In scarlet fever eosinophilia is found from the second or third day of the eruption onward.

6. Chronic myeloid leukemia.

7. Observations on the effect of liver diet in pernicious anemia have recently shown that a marked eosinophilia (20 to 60 per cent) may occur as the blood picture approaches normal.

A diminution in the number of eosinophils (less than 50 per c.mm.) occurs occasionally when there is excessive irritation by parasites. Eosinophils are absent generally in conditions of neutrophilia, as in the acute stages of septic processes and most infectious diseases. Simon designated this association of neutrophilia with eosinopenia as the "septic factor."

BASOPHILIC LEUKOCYTOSIS.—Many hematologists have contended that the basophilic granulocytes are degenerative forms of neutrophils and not living cells. Naegeli holds these opinions to be erroneous. Maximow has observed basophils in bone marrow and has described basophilic myelocytes and mitotic figures. Sabin states that basophils possess the power of locomotion. They are found increased in chronic myeloid leukemia, polycythemia vera, congenital hemolytic anemia, chlorosis, and occasionally in other conditions. Nothing is known concerning the significance of an increase of basophils.

LYMPHOCYTOSIS.—The lymphocytes make up 20 to 30 per cent of the white corpuscles and normally are found to be well within the extreme limits of 1,000 to 3,000 per c.mm. They are only slightly ameboid and take no part in phagocytosis. Lymphocytes possess no oxidative ferments but contain protein and fat-splitting enzymes. Murphy has shown that they are the chief agents in the destruction of tissue grafts and are important in controlling tuberculosis. It is thought that lymphocytes may play a rôle in the production of antibodies and the fixation of toxins. They are increased in healing tuberculosis and markedly diminished in fatal miliary tuberculosis. They may be increased by exposure to ultra-violet light but are unusually sensitive to roentgen rays and radium, exposure to these substances resulting in a diminution in their numbers. Lymphocytopenia may also be encountered in vitamin B deficiency.

An absolute increase in the number of lymphocytes is found in:

1. Infancy. As already mentioned, the blood of infants contains a high proportion of lymphocytes which normally gradually decrease in number. However, any condition which interferes with the proper growth of the child, such as rickets or malnutrition, may inhibit this natural decrease or even cause an increase in lymphocytes.
2. Certain infections, notably whooping-cough. Lymphocytosis is also seen in German measles, undulant fever, mumps (without orchitis) and, as already mentioned, in tuberculosis when the resistance is good.
3. During convalescence lymphocytosis is common.
4. Moderate exposure to dry heat, roentgen rays and sunburn stimulates lymphocyte formation.
5. Lymphatic leukemia.
6. Acute benign lymphadenosis [Infectious mononucleosis] (see Chapter 4, this volume).

Relative lymphocytosis, that is, a relative increase in the proportion of lymphocytes without any increase in the total number of cells, is found in almost all the conditions associated with leukopenia, particularly in the noncoccal infections such as those of the enteric group.

MONOCYTOSIS.—The monocytes constitute 6 to 8 per cent of the leukocytes. Their normal absolute number is 300 to 600 per c.mm. Monocytes are the scavengers of the blood. They move slowly in comparison with neutrophils but serve the important function of taking up damaged red cells or cell fragments, broken-up leukocytes and cell detritus in general. They are therefore spoken of as macrophages. Increases are said to occur in protozoal infections, such as malaria, amebiasis, in typhus, subacute bacterial endocarditis, Rocky Mountain spotted fever, tetrachlorethane poisoning, and occasionally in Hodgkin's disease and syphilis. Naegeli contends that increases or decreases in the number of monocytes accompany increased or decreased activity of the myeloid system.

The comparative readiness with which monocytes and lymphocytes can be differentiated by supravital methods of blood examination has brought out certain interesting and important findings concerning the rôle of the monocyte in tuberculosis. The studies of Sabin, Cunningham and their coworkers suggest that

the tubercle bacillus is able to stimulate the production of monocytes and inhibit the formation of lymphocytes. The monocytes appear to be able to phagocytize tubercle bacilli but in many instances are unable to digest them, and in this way these cells may serve as a useful medium for the growth of the bacilli. Sabin and her associates have found that the monocytes are practically always increased in tuberculosis and that the grade of clinical severity and the extent of dissemination are more or less parallel to the increased number of monocytes. The lymphocytes are related reciprocally to the monocytes. A high ratio of monocytes in proportion to lymphocytes usually means active tuberculous infection and, *vice versa*, reversal of the ratio denotes healing lesions. Although these findings are valuable in diagnosis and prognosis, Cunningham and his co-workers point out that similar changes may occur in other conditions. Monocytes of an epithelioid type, which can be distinguished only by supravital methods, have been seen nowhere but in tuberculosis.

THE PROGNOSTIC VALUE OF THE LEUKOCYTIC BLOOD PICTURE.—Total and differential leukocyte counts afford certain valuable information concerning prognosis. A summary of the full discussion of this subject by Piney is presented here.

1. A slight neutrophilia with slight nuclear shift to the left and persistence of eosinophils is of very favorable significance.

2. A slight or definite leukocytosis with moderate shift to the left (not more than 4 per cent of young forms and 12 per cent of band or "staff" forms) and decrease of eosinophils and lymphocytes signifies a moderately severe infection and should be observed further. Recovery is indicated by:

(1) A falling total leukocyte count with a diminishing proportion of neutrophils; (2) a decrease of immature forms; (3) reappearance or increase of eosinophils; (4) increase in the number of lymphocytes; (5) absence or decrease of toxic or degenerative forms of leukocytes.

Unfavorable signs (Clough) are:

(1) Extremely high total number of leukocytes with very high percentage of neutrophils, and conversely, (2) failure to develop leukocytosis; (3) considerable proportion of immature cells especially if they outnumber the mature forms; (4) absence of eosinophils; (5) marked absolute reduction in lymphocytes; (6) the presence of numerous toxic, degenerative forms.

BIBLIOGRAPHY

- ASHBY, W.: Determination of length of life of transfused blood corpuscles in man, *J. Exper. Med.*, 29: 267-281, 1919.
- BARCHOFT, J.: Alterations in the volume of the normal spleen and their significance, *Am. J. M. Sc.*, 179: 1-10, 1930.
- BLACKFAN, K. D. AND DIAMOND, L. K.: The monocyte in active tuberculosis, *Am. J. Dis. Child.*, 37: 233-243, 1929.
- BROWN, G. O.: Blood destruction during exercise, *J. Exper. Med.*, 36: 481-500, 1922; *ibid.*, 37: 113-130, 187-206, 207-220, 1923.
- BUCKMAN, T. E. AND DARROW, D. C.: An hypothesis concerning the transportation of water in the body, *J. Clin. Investigation*, 1: 582-583, 1925.
- CESARIS-DEMELE, A.: Studies of red blood corpuscles by means of staining in the fresh state, *Folia. Haemat.*, 4: Supplement, 1, 1907.
- COOKE, W. E.: The structure of the human erythrocyte, *Brit. M. J.*, 433, (March 8) 1930.
- AND PONDER, E.: The Polynuclear Count, London, Charles Griffin and Co., 1927.
- CORNER, G. W.: On the widespread occurrence of reticular fibrils produced by capillary endothelium, *Contributions to Embryology*, Carnegie Institute, 9: 83-93, 1920.
- CUNNINGHAM, R. S. AND TOMPKINS, E. H.: The white blood cells in human tuberculosis (as studied by the supravital technique), *Am. Rev. Tuberc.*, 17: 204-239, 1928.
- DOAN, CHARLES A.: The clinical implication of experimental hematology, *Medicine*, 10: 1931.
- ELVEHJEM, C. A., STEENBOCK, H. AND HART, E. B.: Is copper a constituent of the hemoglobin molecule? *J. Biol. Chem.*, 83: 21-25, 1929.
- GARREY, W. E. AND BUTLER, VIRGINIA: The basal leukocyte count and physiological leukocytosis, *Proceedings of the Staff Meetings of the Mayo Clinic*, 4: 157, 1929; *Physiological leukocytosis*, *Am. J. Physiol.*, 90: 355, 1929.
- HARROP, G. A.: The oxygen consumption of human erythrocytes, *Arch. Int. Med.*, 23: 745-752, 1919.
- HILL, A. V.: Function of hemoglobin in body, *Lancet*, 1: 994-998, 1924.
- IZQUIERDO, J. J. AND CANNON, W. B.: Studies on the conditions of activity in endocrine glands, *Am. J. Physiol.*, 84: 545-562, 1928.
- KRUMBHAAR, E. B.: Leukemoid blood pictures in various clinical conditions, *Am. J. M. Sc.*, 172: 519-533, 1926.
- MALLORY, F. B. AND PARKER, F., JR.: Reticulum, *Am. J. Path.*, 3: 515-526, 1927.
- MANN, F. C., SHEARD, C., BULLMAN, J. L. AND BALDES, E. J.: Site of formation of bilirubin, *Am. J. Physiol.*, 74: 497-510, 1925.

- MEVES, F.: Ueber Mitochondrien bezw. Chondriokonten in den Zellen junger Embryonen, *Anat. Anz.*, 31: 399, 1907.
- MURPHY, J. B. AND STURM, E.: Role of lymphoid tissue in resistance to experimental tuberculosis in mice, *J. Exper. Med.*, 29: 35-40, 1919.
- OSGOOD, E. E.: Hemoglobin, color index, saturation index and volume index standards, *Arch. Int. Med.*, 37: 685-706, 1920.
- AND HASKINS, H. D.: Relation between cell counts, cell volume and hemoglobin content of venous blood of normal young women, *Arch. Int. Med.*, 39: 643-655, 1927.
- PEARCE, R. M., AUSTIN, J. H. AND KRUMBHAAR, E. B.: The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice, *J. Exper. Med.*, 16: 383-394, 1912.
- PONS, C. AND KRUMBHAAR, E. B.: Studies in blood cell morphology and function, III. Extreme neutrophilic leukocytosis with a note on a simplified Arneeth count, *J. Lab. and Clin. Med.*, 10: 123, 1924.
- PRICE-JONES, C.: The variation in the sizes of red blood cells, *Brit. M. J.*, 2: 1418, 1910.
- : Red cell diameters in one hundred healthy persons and in pernicious anemia; the effect of liver treatment, *J. Path. & Bact.*, 32: 479-501, 1929.
- ROUS, P. AND ROBERTSON, O.: The normal fate of erythrocytes, *J. Exper. Med.*, 25: 651-663, 1917.
- SABIN, FLORENCE R.: Studies of living human blood cells, *Bull. Johns Hopkins Hosp.*, 34: 277-288, 1923.
- SMITH, C.: Normal variations in erythrocyte and hemoglobin values in women, *Arch. Int. Med.*, 47: 206-220, 1931.
- TOWER, R. W. AND HEAM, C. F.: The intranuclear origin of the mammalian red blood corpuscles observed in living cultures, *Proc. Soc. Exper. Biol. & Med.*, 14: 51, 1916.
- WHIPPLE, G. H.: Pigment metabolism and regeneration of hemoglobin in the body, *Arch. Int. Med.*, 29: 711-731, 1922.
- AND HOOPER, C. W.: Icterus. A rapid change of hemoglobin to bile pigment in the circulation outside the liver, *J. Exper. Med.*, 17: 612-635, 1913.
- WINTROBE, M. M.: Hemoglobin standards in normal men, *Proc. Soc. Exper. Biol. & Med.*, 26: 848-851, 1929.
- : The volume and hemoglobin content of the red blood corpuscle, *Am. J. M. Sc.*, 177: 513-523, 1929.
- : Blood of normal young women residing in a subtropical climate; red cells, hemoglobin, volume of packed red cells, color index, volume index and saturation index, *Arch. Int. Med.*, 45: 277-301, 1930.
- : A study of the correlation of certain characters of the blood with body weight, stature, and surface-area, *Human Biology*, 2: 275, 1930.
- : The direct calculation of the volume and hemoglobin content of the erythrocyte. A comparison with color index, volume index and saturation index determinations, *Am. J. Clin. Path.*, 1: 147-165, 1931.
- AND MILLER, M. W.: Normal blood determinations in the South, *Arch. Int. Med.*, 43: 96-116, 1929.
- WRIGHT, J. H.: The histogenesis of the blood platelets, *J. Morphol.*, 21: 263-278, 1910.

ADDITIONAL BIBLIOGRAPHY

- ASCHOFF, L.: Lectures on Pathology. The Reticulo-endothelial System, New York, Paul Hoeber, 1924.
- BARCROFT, J.: The significance of hemoglobin, *Physiol. Rev.*, 4: 329-351, 1924.
- : The respiratory function of the blood, Cambridge University Press, 1925.
- BARRON, E. S. G.: Bilirubinemia, *Medicine*, 10: 77-133, 1931.
- BUNTING, C. H.: The leukocytes, *Physiol. Rev.*, 2: 505-520, 1922.
- CLOUGH, PAUL W.: Diseases of the Blood, New York and London, Harper & Bros., 1929.
- DOAN, C. A.: The newer aids to diagnosis and prognosis in tuberculosis, *Med. Clin. N. A.*, 14: 279-299, 1930.
- AND ZERFAS, L. G.: The rhythmic range of the white blood cells in human, pathological leucopenic and leucocytic states, with a study of thirty-two human bone marrows, *J. Exper. Med.*, 46: 511-539, 1927.
- DRINKER, C. K.: The Pathological Physiology of Blood Cell Formation and Blood Cell Destruction, Oxford Medicine, Oxford University Press, New York, 2: 509-587, 1920.
- EVANS, C. LOVATT: Recent Advances in Physiology, Ed. 3, Philadelphia, P. Blakiston's Son & Co., 300-333, 1928.
- FARLEY, D. L., ST. CLAIR, H. AND REISINGER, J. A.: The normal filament and nonfilament polymorphonuclear neutrophil count, *Am. J. M. Sc.*, 180: 336, 1930.
- HEWLETT, ALBION W.: Pathological Physiology in Internal Diseases, Ed. 3, New York and London, D. Appleton & Co., 325-327, 551-575, 1928.
- KRUMBHAAR, E. B.: Functions of the spleen, *Physiol. Rev.*, 6: 160-200, 1926.
- MAXIMOW, A. A.: Relation of blood cells to connective tissues and endothelium, *Physiol. Rev.*, 4: 533-563, 1924.
- MUNSER, J. H., JR.: The leukocytes after hemorrhages, *Am. J. Med. Sc.*, 162: 40-46, 1921.
- PINEY, A.: Recent Advances in Haematology, Ed. 2, London, J. & A. Churchill, 1928.
- REZNICKOFF, P.: Immature white blood cell counts in infectious diseases, *J. Am. M. Ass.*, 93: 963-967, 1929.
- RICH, A. R.: The formation of bile pigment, *Physiol. Rev.*, 5: 182, 1925.
- ROUS, P.: Destruction of the red blood cells, *Physiol. Rev.*, 3: 75-105, 1923.
- ROWNTREE, LEONARD G., BROWN, GEORGE E. AND ROTH, GRACE M.: The Volume of the Blood and Plasma in Health and Disease, Philadelphia, W. B. Saunders Co., 1929.
- SABIN, FLORENCE R.: On the origin of the cells of the blood, *Physiol. Rev.*, 2: 38-69, 1922.
- SACKS, B.: The reticulo-endothelial system, *Physiol. Rev.*, 6: 504-545, 1926.
- SCHILLING, VICTOR: Translated by R. B. H. Gradwohl; The Blood Picture and Its Clinical Significance, Ed. 7 & 8, St. Louis, C. V. Mosby Co., 1929.
- SCHNIDER, E. C.: Physiological effects of altitude, *Physiol. Rev.*, 1: 631-659, 1921.
- WINTROBE, M. M.: The erythrocyte in man, *Medicine*, 9: 195-255, 1930.

CHAPTER II

THE TECHNIC OF BLOOD EXAMINATIONS

By JOHN H. MUSSER, M.D., AND MAXWELL M. WINTROBE, M.D.

Obtaining the specimen, p. 769.

Cell counting, hemoglobin and hematocrit determinations, p. 771—Enumeration of the red corpuscles, p. 771—Enumeration of the white corpuscles, p. 775—Estimation of hemoglobin, p. 776—Direct methods, p. 776—Acid hematin methods, p. 778—Carbon monoxide methods, p. 781—Oxygen capacity method, p. 781—Iron content method, p. 781—Other methods, p. 781—Determination of the volume of packed red cells or relative cell volume, p. 781.

Determination of the size and hemoglobin content of red corpuscles, p. 783—Determination of the size of the red corpuscles, p. 783—Cell diameter, p. 783—Measurement of corpuscular volume, p. 784—Volume index, p. 784—Mean corpuscular volume, p. 785—Mean corpuscular thickness, p. 785—Estimation of the hemoglobin content of the red corpuscle, p. 785—Color index, p. 785—Mean corpuscular hemoglobin, p. 785—Saturation index, p. 785—Mean corpuscular hemoglobin concentration, p. 786—Relative value of the indexes and direct calculations of the volume and hemoglobin content of the red corpuscles, p. 786.

The microscopic examinations, p. 786—Care and preparation of slides and cover-glasses, p. 786—Examination of fresh blood, p. 786—Making the blood smear, p. 786—Fixation of dried preparation, p. 788—Staining of the blood smear, p. 788—The differential leukocyte count, p. 789—Peroxidase staining, p. 790—Enumeration of reticulocytes, p. 791.

Examinations concerned with coagulation, p. 791—Enumeration of the blood platelets, p. 791—Bleeding time, p. 792—Retraction time of blood clot, p. 792—Coagulation time, p. 792—Prothrombin time, p. 793—Calcium time, p. 793.

The estimation of increased blood destruction, p. 794—The study of the pigment metabolism, p. 794—Determination of the fragility of erythrocytes, p. 794.

Miscellaneous examinations, p. 794—Specific gravity and viscosity of blood, p. 794—The sedimentation rate of corpuscles, p. 795.

Obtaining the Specimen.—For the usual clinical examinations blood may be obtained in sufficient quantity *from the finger or the lobe of the ear*, or, in the case of infants, the plantar surface of the heel. The part to be punctured is first cleansed with alcohol and rubbed dry. Unless the skin at the site of the puncture is dry, the blood will not form a rounded drop. An edematous area or one in which local cyanosis is marked should be avoided in obtaining specimens for examination. The former yields diluted blood, the latter a misleadingly concentrated specimen. In the ear the edge of the lobe should be punctured. If the finger is preferred the wound should be made in the side or back of the finger, between the nail and the first joint, as these situations are much less sensitive than the ball of the finger. The part to be punctured should be held firmly between the thumb and forefinger of the operator.

For making the puncture an instrument with a sharp cutting edge should be used. A Hagedorn needle (no. 6) or a blood lancet, the bevelled portion of which is not too long and narrow, is most suitable (Fig. 4). Ordinary needles are poor substitutes. A Hagedorn needle may be conveniently carried by fixing it in the cork of a small vial. Some workers use a piece of broken cover-glass which is firmly grasped between the finger and thumb at the point required to permit necessary penetration and at the same time to limit the depth of the

puncture. The automatic blood lancet (Fig. 5) is the most satisfactory instrument of all. The instrument used should be cleansed with alcohol.

The puncture itself should be made with a quick stroke and must be sufficiently deep to produce a spontaneous flow of blood. Pressure must be avoided as this will cause dilution of the blood by tissue fluid. The first drop or two of blood should be discarded.

When larger quantities of blood are required than can be obtained in this manner, it is necessary to *puncture a vein*. The veins in the bend of the elbow are most suitable for this purpose as they are large, conveniently situated and less likely to roll beneath the needle. The area to be punctured is wiped with 70 per cent alcohol or painted with tincture of iodine. Any convenient tourniquet, such as a piece of rubber tubing or the cuff of the sphygmomanometer, is fixed about two inches above the bend of the elbow. It is so adjusted that a slight pull will promptly release it. If the veins are not readily seen after the tourniquet has been tied, the patient may be instructed to open and close his fist a few times. In obese patients the veins are often more readily felt than seen. The tourniquet should be applied neither too tightly, thus cutting off the arterial flow, nor for longer than two minutes since the blood in such cases will become altered in concentration.



FIG. 4

FIG. 4.—GOOD BLOOD LANCET. (Bass and Johns, Practical Clinical Laboratory Diagnosis, Williams and Wilkins Co.)



FIG. 5

FIG. 5.—AUTOMATIC BLOOD LANCET. (Courtesy of Hellige, Inc.)

A clean dry syringe to which a 20 or 22 gauge, sharp, sterile hypodermic needle is attached, should be used to draw the blood. The bevel of the needle should be short as otherwise, when the vein is very superficial, the point of the needle may be within the vein while the proximal end of the bevel is still outside the skin. The forearm of the patient is steadied with one hand and the skin over the vein drawn tense by means of the thumb while the needle is inserted beneath the skin with the other. The syringe should be so held that the bevel of the needle is pointed sideways. After the skin has been punctured, the needle is inserted into the vein. It is better not to puncture the vein and the skin at the same point.

After sufficient blood has been withdrawn, the tourniquet is released, and only after this has been done is the needle withdrawn. Unless this precaution is observed, a hematoma will be produced. Simple pressure by means of a piece of sterile gauze is sufficient to stop the flow of blood from the puncture wound.

If coagulation is to be prevented, the blood obtained in this way may be placed in a vial* in which 20 per cent solution of potassium oxalate, in the ratio of one drop for every 5 c.c. of blood collected, has been placed and allowed to dry. If the dropper employed is one that will deliver 20 drops to the cubic centimeter, each drop of this oxalate solution will contain approximately 10 mg. of potassium oxalate, a quantity which is just sufficient to prevent the coagulation

* A small vial such as that shown in Fig. 4 will be found very convenient. The vial should be fitted with a cork so that the blood can be thoroughly mixed immediately before a sample is withdrawn for examination. Such a vial will be found more suitable than a test tube as samples can be readily withdrawn into cell counting pipets directly from the vial.

of 5 c.c. of blood. It is advisable to use as little oxalate as is necessary and it is useful to know the amount employed since a slightly hypertonic solution is produced by the addition of this salt to the blood. When used in the quantity recommended, the alterations are negligible so far as the red cell count and hemoglobin content of the blood are concerned, and these determinations, as well as leukocyte, platelet and reticulocyte counts, may be conveniently made on the blood so collected. Shrinkage in cell volume of approximately 5 per cent, however, is produced and appropriate correction for this should be made in hematocrit determinations. Before emptying the syringe into the vial the needle should be removed as hemolysis may result from forcing the blood through the needle.

THE USE OF VENOUS BLOOD IN HEMATOLOGICAL STUDIES.—When several blood examinations are to be carried out it will frequently be found more satisfactory to collect 5 c.c. of blood from a vein and examine it at the convenience of the observer in the laboratory. That blood counts carried out on venous blood are as accurate as counts on capillary blood has been repeatedly proven. If the precautions in making a venipuncture already mentioned are observed, results of examinations of venous blood will be found more consistent and accurate than those carried out on capillary blood as errors due to manipulation or constriction of the finger or ear, edema, congestion and the like, can be completely done away with. Furthermore, doubtful counts can be readily repeated when 5 c.c. of blood are at hand, and any additional blood studies which the preliminary examination may indicate can conveniently be carried out. The oxalated venous blood may be used for erythrocyte, leukocyte, platelet and reticulocyte counts, hemoglobin and hematocrit determinations, icterus index, van den Bergh, fragility and sedimentation tests, and even blood smears may be made. Blood may be taken at the same time for determination of the coagulation time, clot retraction rate, Wassermann, and other hematological, chemical or serological studies. It is best to examine the oxalated blood within about 3 hours of its withdrawal from the patient although, according to Osgood, red and white cell counts and hemoglobin estimations are accurate if done within 24 hours.



FIG. 6

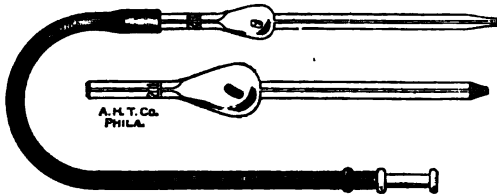


FIG. 7

FIG. 6.—RED CELL THOMA PIPET.

FIG. 7.—TRENNER PIPETS. (Courtesy of Arthur H. Thomas Co.)

CELL COUNTING, HEMOGLOBIN AND HEMATOCRIT DETERMINATIONS

The Enumeration of the Red Corpuscles.—The *PRINCIPLE* of the methods for counting the cells of the blood consists in the accurate dilution of a known quantity of blood and the enumeration of the number of cells seen in a given volume. For such determinations a diluting pipet, a diluent and a counting chamber are required.

The *Thoma diluting pipet* (Fig. 6) consists of a capillary tube graduated in tenths, which opens into a bulb containing a glass bead. In the pipet used for counting the number of red cells the bulb, when filled to the mark above it (101) will hold 100 times the quantity of fluid contained in the 10 divisions of the capillary tube.

Trenner has devised what is known as an *automatic pipet* (Fig. 7), an instrument which has several advantages as compared with the Thoma pipet. It consists of a capillary tube which ends abruptly in a bulb, the sides of which meet the capillary portion at right angles. The capillary volume is adjusted to

exactly 1/200 of the content of the bulb in the red cell pipet. As will be described later, accurate dilution is more easily carried out by means of this instrument.

The Diluent.—Any solution employed as a diluent must possess two qualities, namely, it must prevent coagulation and it must be isotonic. The most commonly used solutions are those devised by Hayem* and by Toison.† The specific gravity of Toison's fluid is higher than that of Hayem's solution and therefore the red corpuscles do not settle out so readily. Besides, the white corpuscles are stained blue and therefore can be distinguished and enumerated in the same preparation as the red cells. The chief disadvantage of Toison's solution is that fungi grow in it rather readily, a fact which necessitates frequent filtering. The growth of fungi may be inhibited by placing several crystals of thymol in the solution after it has been prepared.

The Counting Chamber.—Several types of counting chamber with a variety of different rulings have been recommended. The one which is most commonly employed is the *Bürker type* (Fig. 8) with double *Neubauer ruling*. The counting chamber is a heavy glass slide in the center of which are two ruled platforms. These are separated from each other by a transverse moat and from a longitudinal, elevated bar on each side by a longitudinal moat. These lateral bars are so ground that a cover-slip resting on them lies exactly 0.1 mm. above the ruled platforms. On each platform is engraved a ruled area 3 mm. on each side (9 mm. square). This area is divided into 9 large squares which are again subdivided, the 8 outside squares being subdivided into 16 smaller squares whereas the central square is subdivided into 400 small squares. Each of the large squares is 1 mm. on the side, or 1 sq. mm. in area. Each of the medium



FIG. 8.—LEVY-NEUBAUER COUNTING CHAMBER. (Courtesy of Arthur H. Thomas Co.)

squares is 0.25 mm. on the side, while each of the small squares is 0.05 mm. on the side or 0.0025 sq. mm. in area. In the original Neubauer ruling the 400 smallest squares in the central square millimeter are arranged into 16 groups of 25 small squares each by means of an extra line in the middle of every fifth square (Fig. 9a). In the improved ruling a "split" boundary line divides the central square millimeter into 25 groups of 16 squares (Fig. 9b).

The *Levy-Hausser* counting chamber (Fig. 10) is similar to the one just described in that the Neubauer ruling is likewise engraved upon it. It has the advantage of being mounted in a bakelite holder and is therefore less easily broken.

A more simple ruling has been devised by *Bass* (Fig. 11). It consists of a square 2 mm. on the side which is divided into 10 rectangles, 0.2 mm. by 2 mm. At each corner and in the center are superimposed squares of 0.2 mm. side, each of which is further divided into 16 small squares of 0.05 mm. side. The five superimposed squares are used for the enumeration of red cells, the ten rectangles for the enumeration of white cells. Johns has added 15 more rectangles to the original ten of the Bass ruling, an improvement which facilitates the counting of spinal fluid when there are few cells.

PROCEDURE IN COUNTING RED BLOOD CORPUSCLES.—When the Thoma "101" pipet is used, blood is drawn by suction to the mark 0.5. This must be done with care for if there is much excess of blood above the mark, even though this excess be drawn down, enough blood will adhere to the sides of the pipet to vitiate

* Hayem's fluid consists of an aqueous solution of mercuric chloride (0.25 per cent), sodium sulphate (2.5 per cent) and sodium chloride (0.5 per cent).

† Toison's solution contains methyl violet (5 B 0.025 gm.), sodium chloride (1 gm.), sodium sulphate (8 gm.), neutral glycerin (30 c.c.) and distilled water (160 c.c.).

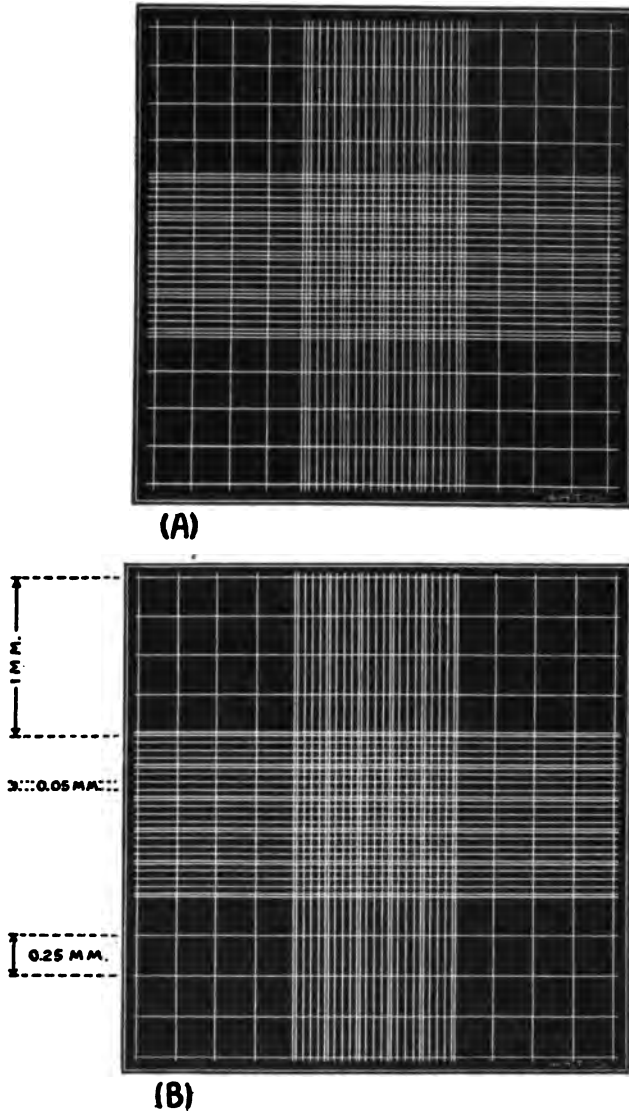


FIG. 9.—NEUBAUER RULING—(a) OLD, AND (b) NEW. (Courtesy of Arthur H. Thomas Co.)

the results. However, if the blood passes the mark only slightly the excess may be drawn down by touching the tip of the pipet with the finger or a blotter. The blood adhering to the outside of the pipet is next wiped off and the diluent is drawn in until it fills the bulb and reaches the mark 101. The procedure up to this point should be carried on without delay in order to avoid coagulation of the blood in the capillary portion of the pipet.

While drawing in the diluent the pipet is revolved between the finger and the thumb in order to mix the blood thoroughly with the diluent. After the desired quantity of solution has been drawn into the pipet, it is held horizontally and shaken for about one-half minute in order to secure thorough mixing. For this purpose the pipet may be held loosely in one hand while the attached rubber

tubing is revolved between the thumb and forefinger of the other hand. Shaking constantly in any one direction should be avoided. The mixing should be repeated each time before expelling a drop for examination.

By drawing blood to the 0.5 mark and diluting fluid to the 101 mark, a mixture of blood diluted 1:200 is obtained. This is the dilution most often employed. In cases of severe anemia greater accuracy will be secured if the blood is drawn to the 1 mark and the diluent to 101. In such a case a dilution of 1:100 is obtained.

To fill the Trenner automatic pipet, blood is drawn into the pipet until the lumen is at least three-fourths full. Suction is then discontinued and, if the pipet is being held in a horizontal position, blood will continue to rise until it



FIG. 10

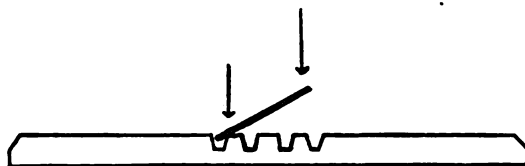


FIG. 12

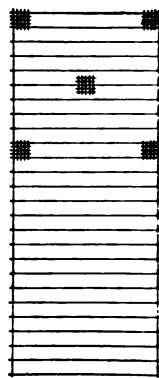


FIG. 11

FIG. 10.—LEVY-HAUSER COUNTING CHAMBER. (Courtesy of Arthur H. Thomas Co.)

FIG. 11.—BASS-JOHNS RULING. (Courtesy of Bausch and Lomb Optical Co.)

FIG. 12.—TO SHOW METHOD OF APPLYING COVER-GLASS.

reaches the extremity of the capillary where it automatically stops. The diluent is then drawn up as with the Thoma pipet. A dilution of 1:200 is secured by the use of this pipet. It has the obvious advantage of great precision and ease in the drawing up of blood.

Before the diluted blood is placed on the counting chamber, about one-third is first expelled and discarded. A small drop is then placed on the ruled portion of the counting chamber. The cover-glass is next put into place over the drop of blood. This is most conveniently done by first tilting one side of the cover-glass by the pressure of a finger into the groove outside one of the supporting bars. The cover-glass is then slowly brought down over the drop of blood by pressure on its unsupported side (Fig. 12). If the cover-glass has been properly adjusted, concentric color rings ("Newton's rings") will be visible when the surface of the applied cover-slip is held toward the light at, or slightly below, the level of the eyes.

The drop of diluted blood should just fill the ruled platform without running over into the moat around it. Some workers prefer to first place the cover-glass in position on the counting chamber and then, by placing a small quantity of diluted blood in the angle between the cover-glass and the ruled platform, the blood is allowed to run under the cover by capillary attraction. Clamps may be used to keep the cover-glass in place.

After a few minutes have been allowed for the blood to settle, the slide is examined to ensure even distribution of the cells in the chamber. If distribution is satisfactory, the cells are counted. The high power objective of the microscope should be used. In the Neubauer ruling the small squares in the central square millimeter are employed in the enumeration of red cells. When the original Neubauer ruling is used the red cells in the four corner groups of 25 small squares are counted. In the improved Neubauer chamber the number of cells in the four corner groups of 16 squares and in one central group is re-

corded. In the Bass-Johns chamber the five small squares are used in red cell counting. In making the counts all corpuscles touching the lines at the upper and left side of each square are counted while those touching the bottom and right side are not included.

CALCULATION.—The number representing the total number of cells counted must be multiplied by the dilution of the sample and must also be corrected for the volume examined in order that the result will represent the number of cells in 1 c.mm. The smallest squares counted have an area of 0.0025 sq. mm. and are 0.1 mm. deep, being thus 0.00025 c.mm. in volume. With the original Neubauer ruling, 100 such squares are counted, a total volume of 0.025 c.mm. If the dilution is 1:200, the number of cells counted must therefore be multiplied by 40×200 or 8000 to give the value for 1 c.mm. With the improved Neubauer ruling 80 small squares are counted, a volume of 0.02 c.mm. For dilutions of 1:200, then, the number of cells counted must be multiplied by 50×200 or 10,000. This is done simply by adding 4 zeros to the total cells in the count. When the Bass-Johns ruling is used, the same factor is employed. When the dilution is 1:100 the number of cells counted is multiplied by 5000.

It is obviously important for successful enumeration of cells that all apparatus be clean and free from dust or grease. Pipets should be thoroughly washed with water, alcohol and then ether, these being added in amounts equivalent to at least three fillings of the pipet with each liquid. The counting chamber is washed with water or, if cement has not been used in its construction, it may be conveniently wiped with alcohol. From time to time pipets, cover-slips and counting chambers (if cut from one piece of glass) should be washed with pure nitric acid or sulphuric acid to remove any traces of blood protein that may accumulate. Acid should be carefully washed away before the instruments are again used. A horsehair—never a wire—should be used in removing blood which has clotted in the pipets. Alcohol or acid should never be used on the cemented type of counting chamber.

It is preferable to use counting chambers, pipets and cover-slips certified by the Bureau of Standards. It is important to realize that unless care is taken, the error of the cell count may be very great. Even when unusual care is employed the probable error of red cell counts amounts to 2 to 4 per cent. The probable error should be borne in mind in comparing and evaluating such counts.



FIG. 13.—WHITE CELL THOMA PIPET.

The Enumeration of the White Corpuscles.—If Toison's solution is used as the diluent, the white corpuscles may be counted in the same preparation as are the red cells, since they are stained by the dye contained in Toison's fluid and are easily distinguished from the red corpuscles. If the Neubauer ruling is used, the number of white corpuscles in each of the four large corner squares is counted, a total volume of 0.4 c.mm. ($4 \times 1 \times 1 \times 0.1$) being examined in this way. With the Bass-Johns ruling the number of white corpuscles in 10 rectangles, likewise a total volume of 0.4 c.mm., is counted. If the blood dilution has been 1:100, the number of cells counted must be multiplied by 250 to give the value per cubic millimeter. The readiness with which fungi which resemble leukocytes grow in Toison's fluid vitiates the value of this method of enumerating the white corpuscles. Furthermore, since the dilution of the blood is relatively great, accuracy is sacrificed for simplicity.

For the more accurate enumeration of the white corpuscles, special pipets and diluting fluids are recommended. These special "white cell pipets" permit a dilution of blood of only 1:10 or 1:20, and consequently much greater accuracy is thus attained. Either Thoma (Fig. 13) or Trenner pipets (Fig. 7) for this dilution may be purchased. As a diluent 3 per cent acetic acid is used. This solution dissolves the red corpuscles. It may be colored with gentian violet (Türk's solution) which renders the leukocytes more clearly visible. The Thoma pipet is filled with blood to the 0.5 mark and with diluting fluid to the 11 mark.

This gives a dilution of 1:20. If preferred, the Trenner "white cell pipet" may be used. After the diluted blood has been thoroughly mixed a few drops are expelled from the capillary portion of the pipet and one drop is then placed on the counting chamber in the manner already described.

If acetic acid has been used, only white corpuscles will be seen under the microscope. If Toison's fluid is used, the leukocytes appear as blue cells of various sizes and are easily distinguished from the red corpuscles. All the white cells in the four large corner squares of the Neubauer ruling or in the ten rectangles of the Bass-Johns ruling are counted.

As each of the squares is 1 mm. to the side and 0.1 in depth, the cells in a total volume of 0.4 c.mm. are counted in this way. To determine the value for number of leukocytes per cubic millimeter, therefore, the number of cells counted is divided by this volume (0.4) and multiplied by the dilution (20) or, more simply, is multiplied by 50. To ensure accuracy two or, better, four separate counts should be made and the final value determined by averaging the two or four estimations.

The Estimation of Hemoglobin.—Although the determination of the amount of hemoglobin is one of the most important of all the chemical tests of the blood, it is nevertheless true that, probably because of the general usefulness and importance of hemoglobin determinations and the need for a simple and readily available technic, the hemoglobin of the blood is as a general rule determined with less care and by methods which are more inaccurate than those for the determination of any other constituent of the body. Although a large number of instruments and methods is at present available, it cannot be said that any one of them is entirely satisfactory.

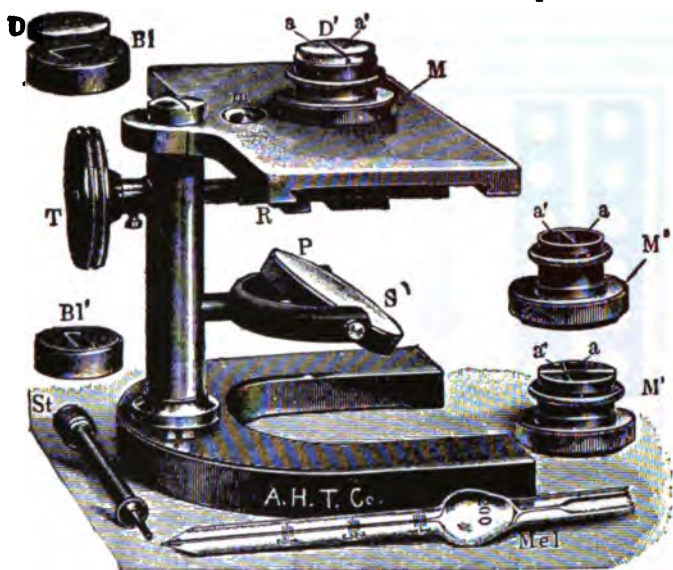
The majority of the instruments employed at present give values for hemoglobin in proportion to an arbitrarily set "normal" quantity of hemoglobin in the blood of healthy adults. Although such a method of expressing values has its obvious advantages, it is very difficult to fix a single "normal" value for hemoglobin in view of the well known variation in the quantity of hemoglobin in respect to age, sex and other factors already discussed in Chapter I, this section. Furthermore, until recently no large series of blood determinations has been available for the fixation of normal standards and, in fact, in view of the variations already mentioned, even further accurate determinations are desirable. This lack of accurate standards has resulted in the employment as the equivalent of 100 per cent of hemoglobin for the various instruments, values ranging from 13.8 gm. to 17.2 gm. and even 21 gm. per 100 c.c. of blood. This deplorable lack of uniformity makes it difficult to compare hemoglobin values determined by different instruments. Matters are still further aggravated by a rather general carelessness on the part of the manufacturers in the calibration of instruments. For these reasons there is now an increasing tendency to report hemoglobin values directly in grams per 100 c.c. of blood, a tendency which will undoubtedly make for greater accuracy. A number of instruments now give hemoglobin values directly in grams as well as in per cent. Normal values for hemoglobin have been given in Chapter I.

(a) **DIRECT METHODS FOR THE ESTIMATION OF HEMOGLOBIN.**—A number of methods are employed which depend on the comparison of whole or diluted blood with various color scales.

Gower's Hemoglobinometer.—The principle of this instrument, devised in 1878, consists in the dilution of a known quantity of blood with water until the color of the solution matches that of a standard picrocarmine solution. The figures on the graduated tube indicate the percentage of hemoglobin. The standard tube is apt to fade in color at a varying rate. This instrument is now of only historical interest.

Fleischl-Miescher Hemoglobinometer (Fig. 14).—Blood diluted with water to a given volume is placed in a cell and compared in color to a wedge-shaped piece of colored glass which can be moved by a milled screw until the colors match. This instrument is relatively accurate but is little used because of its costliness. One hundred per cent is equivalent to 15.8 gm. of hemoglobin per 100 c.c. of blood.

Oliver's Hemoglobinometer (Fig. 15).—Blood diluted in a small cell is compared in color with a series of standards of definite graduations contained in wooden blocks. This instrument is little used and has no special advantages.



Courtesy of A. H. Thomas & Co.

FIG. 14.—FLEISCHL-MIESCHER HEMOGLOBINOMETER.

Description.—Milled wheel at left (T) moves a tinted glass wedge (R) under the fixed metal stage surmounted by double chamber reservoir which receives light from the calcium sulphate reflecting disc (PS) below. Half of the same chamber is filled with the diluted blood contained in the measuring capillary pipet (Mel). The other contains only plain water but receives its light from the colored wedge. By moving the wedge back and forth the colors are matched and the percentage reading is shown on a scale visible through the opening (M) just in front of the supporting upright. The blood is obtained in exactly the same manner as for a blood count, the diluent being calcium carbonate solution (0.1 per cent) and the tube permitting the observer to use dilutions of 1:200, 1:300 or 1:400 according to the diluting height to which the blood column is allowed to rise (marks 1/1, 2/3, 3/4 respectively) before diluting and thoroughly mixing. Increased accuracy is obtained by the use of a grooved cover-glass (D') which fits over the slightly raised partition dividing the two chambers, which must each be so filled as to present a convex meniscus. The necessary narrowing of the field is secured by cap-diaphragm (Bl'). The average of at least ten determinations is required for accurate work.

Tallqvist's Hemoglobin Scale.—This, the simplest and least reliable instrument, consists of lithographed color bands which represent the color of blood in dilutions running from 10 per cent to 100 per cent. A drop of the patient's blood is taken up by absorbent paper, the resulting stain is placed under the central perforation of the color bands and comparison is made as soon as the stain has lost its wet gloss. One hundred per cent by this instrument is supposed to represent 15.8 gm. of hemoglobin per 100 c.c. of blood.

This is a simple, rapid but inaccurate method. The instrument has been shown to be susceptible to errors ranging from 2 to 40 per cent. Readings below 60 per cent are little more than a guess. The simplicity of the method is an advantage, it is true, but so unreliable is it that its use can be condoned only if the same scale is being used by the same observer in following closely the same patients. Gross relative changes in hemoglobin are indicated in this way, but not absolute values.

Dare's Hemoglobinometer (Fig. 16).—A circular disc of tinted glass, representing variations in blood coloring matter of a known degree, is brought into

contrast by transmitted candle or electric light with a film of fresh whole blood drawn by capillary attraction between two glass plates, one transparent, the other translucent and white. A detachable observation tube and a circular shield protect the eyes from extraneous light. The percentage of hemoglobin may be read directly from a scale. One hundred per cent represents 13.77 gm. of hemoglobin per 100 c.c. of blood.

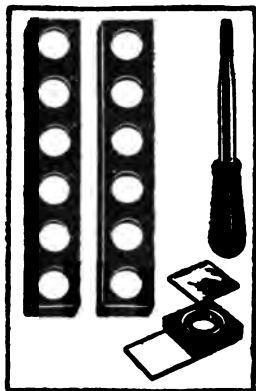


FIG. 15

FIG. 15.—OLIVER'S HEMOGLOBINOMETER. The discs shown as white in the illustration are colored to represent the various blood dilutions and direct comparison is made with a solution of the actual blood obtained by a measured mixing capillary pipet furnished with the instrument. Intermediate readings are obtained by placing squares of tinted glass over the fluid under examination.



FIG. 16

FIG. 16.—DARE'S HEMOGLOBINOMETER. (Courtesy of Will Corporation.)

The Dare instrument is very popular and is probably the most useful of all the instruments in which blood is matched directly. It is, however, quite costly and gives readings which are accurate to only 20 or 30 per cent. It is more useful for values below 65 per cent hemoglobin; above this value it is very misleading. All the instruments of this group are open to the objection that shades of red are difficult to match. With the Dare instrument the presence of excessive carbon dioxide in the blood to be examined may add to this difficulty.

(b) ACID HEMATIN METHODS.—By diluting blood with 0.1 N hydrochloric acid, acid hematin which is a brown suspension is formed. The color of acid hematin is more easily matched than is that of blood itself. The principle has been adopted in a number of instruments.

Sahli Hemoglobinometer (Fig. 17).—The empty graduated tube of the instrument is filled to the mark 10 with a decinormal solution of hydrochloric acid. Blood, drawn into a measuring pipet, is then added and thoroughly mixed with the acid. A brown suspension of acid hematin is formed. Distilled water is then added, drop by drop, until the color of the solution in the graduated tube corresponds to that of the standard tube. The original standard in this instrument was a solution of acid hematin corresponding to 17.2 gm. of hemoglobin and was contained in a sealed glass tube. As the color of acid hematin eventually fades on standing, this standard has been replaced in the newer instruments by a rod of colored glass which is said to be permanent in color. This newer standard is not matched quite as readily as in the acid hematin standard, although the match is usually quite good.

The pipet used for measuring blood is so calibrated that more or less blood may be employed according to the degree of anemia of the subject. Since low values are difficult to read, this modification is of great advantage.

Hellige-Normal Hemometer (Fig. 18).—This instrument, a modification of the Sahli hemoglobinometer already described, has several advantages in comparison with the latter. Only a small part of the graduated tube and the glass

standard is shown, and the standard rods and tube are not separated by bakelite. Moreover, the new diluting tube which has recently been prepared is square rather than round and has the advantage that it may be set in the hemometer in such a position that the graduations cannot be seen. All these factors greatly facilitate the color reading. Graduated tubes may be secured on which gram values as well as values in per cent of hemoglobin, based on 14.5 gm. per 100 c.c. of blood as the equivalent of 100 per cent, are marked.



FIG. 17.—SAHLI HEMOGLOBINOMETER. (Courtesy of Will Corporation.)

Newcomer Hemoglobinometer (Fig. 19).—Newcomer employs a disk of light brown glass approximately 1 mm. thick as the color standard. A special Newcomer hemoglobinometer may be purchased or the disk alone may be secured and placed in one of the light paths of any colorimeter of the Duboscq type. Only a small quantity of blood, about 0.01 c.c., is required. It is drawn into a special pipet and diluted with 1 per cent hydrochloric acid, and the acid hematin formed in this way is matched in the colorimeter. Since the pipets supplied contain only a total of about 5 c.c., colorimeter cups of this size must be used. Although the Newcomer hemoglobinometer is itself quite expensive, the disk and pipets are not costly and therefore the method is readily available to laboratories already equipped with a colorimeter.

The acid hematin methods are preferable to the direct methods of hemoglobin estimation. The match is more easily made, the results are more accurate and the instruments are not expensive. Operation is simple and relatively quick. For ordinary clinical work these methods are satisfactory although several defects should be considered if a high degree of accuracy is desired.

(1) The instruments are not all well, or uniformly, standardized. This criticism applies to the more expensive Newcomer hemoglobinometer as well as to the Sahli. It is possible, however, to restandardize these instruments, since their error is more or less uniform in degree. Especially is this true of the Newcomer hemoglobinometer by means of which readings can be more easily made than with the Sahli or Hellige hemometers. Restandardization is most easily carried out by comparison with an instrument of known accuracy or by making readings on the blood of a number of individuals who are known to be in good health and whose blood contains 5,000,000 red corpuscles per cubic millimeter. A correction factor can then be worked out and all future readings multiplied by this factor. Greatest accuracy is secured by comparison with hemoglobin readings determined by the Van Slyke oxygen capacity method.

(2) The color of an acid hematin preparation gradually increases in intensity. Since this increase in color follows a definite law, however, a reasonably accurate correction may be calculated. About 95 per cent of the color is attained after 10 minutes and after one-half to one hour the change is insignificant. The intensification may be hastened by immersing the acid hematin in a water bath



FIG. 18

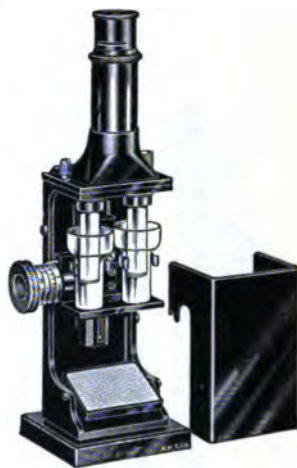


FIG. 19

FIG. 18.—HELLIGE-NORMAL HEMOMETER. (Courtesy of Hellige, Inc.)

FIG. 19.—NEWCOMER HEMOGLOBINOMETER. (Courtesy of Arthur H. Thomas Co.)

at 56° C. for 7 minutes. The objection that this causes the production of some cloudiness in the suspension has, however, been raised against this procedure. Whatever provision is made concerning this intensification of color, it should be borne in mind that it is important to follow a uniform procedure in making readings on acid hematin preparations.

(3) It has already been mentioned that the color of acid hematin standards fades in time and that the colored glass which has been substituted for these standards does not permit perfect matching. For these reasons various modifications of the methods described have been suggested.

Cohen and Smith Standard.—A large sample of blood is secured, its oxygen capacity determined, and the hemoglobin content calculated on the basis of the Haldane figure, namely, that 1 volume per cent of oxygen is the equivalent of 0.746 gm. hemoglobin. The blood is then diluted with 0.1 N hydrochloric acid to make a 3 per cent suspension. This stock suspension will keep for three months. A standard is made up each week by diluting 5 c.c. of the stock to 200 c.c. with 0.1 N hydrochloric acid.

Terrill recommends a concentrated suspension of acid hematin and has also prepared a dried powder which can be weighed out accurately and dissolved to form a standard acid hematin. These preparations, it is claimed, are more stable than are simple acid hematin suspensions. *Jacobson* advocates the use of rutigallie acid solutions as a substitute for the brown color of acid hematin. *Osgood and Haskins* have prepared a standard from ferric and chromic sulphate which has not faded in eight years.

Care should be taken in making readings by means of any of the instruments already described to use a uniform source of light. In making comparisons, several rapid readings should be made and the average of these taken; otherwise the eye will become fatigued and the reading will be erroneous.

(c) **CARBON MONOXIDE METHODS.**—The original carbon monoxide method devised by Hoppe-Seyler in 1892 was later adapted for use with the Gower hemoglobinometer by Haldane. Hemoglobin is converted into carbon monoxide hemoglobin by the addition of coal gas and its color compared with that of a known standard. Palmer has modified the technic for use with the Duboseq colorimeter. The method is quite accurate but the standard must be freshly prepared each month as Robschait has shown that the standard suspensions deteriorate. She has applied Palmer's procedure to Sahli's principle with satisfactory results.

(d) **OXYGEN CAPACITY METHOD.**—The Van Slyke modification of Haldane and Smith's method of determining the oxygen capacity of blood as a measure of its hemoglobin content is probably the most accurate method of hemoglobin determination at present available; this method is employed in the accurate standardization of hemoglobinometers. A known quantity of blood is saturated with oxygen which is then liberated and measured by means of Van Slyke's complex and expensive apparatus. The hemoglobin content of the blood is calculated on the basis of 1 volume per cent of oxygen as the equivalent of 0.746 gm. of hemoglobin, a value which is based on the work of Haldane. Considerable experience is necessary for proper determinations by this method.

(e) **IRON CONTENT METHOD.**—Wong has described a colorimetric method for the quantitative estimation of iron in the blood. Hemoglobin content is calculated on the assumption that iron forms 0.334 per cent of the total weight of hemoglobin. Berman, Fowweather and Dupray have modified the original method but it is still a time-consuming procedure. Its accuracy is, however, quite high and the method is useful as a means of standardization when the elaborate Van Slyke apparatus is not available.

(f) **OTHER METHODS** of hemoglobin determination are either now discarded or not sufficiently generally used to require more than mentioning here. Williamson used a spectrophotometer for his large series of determinations in 1916. More recent determinations suggest that his values are quite accurate. The refractometer and extincitometer have also been used for hemoglobin estimation. Schwentker has recently described a spectroscope which is said to be quite simple in operation and very accurate. Sheard and Sanford have devised a photo-electrometer for use in hemoglobin estimation.

Determination of the Volume of Packed Red Cells or "Relative Cell Volume."—For the determination of the relative volume occupied by the red corpuscles, several instruments are available.

Daland Hematocrit.—The apparatus (Fig. 20) consists of two graduated capillary tubes and a small hand centrifuge. The capillary tube is filled with blood and, before coagulation has taken place, is centrifugated for 3 minutes as rapidly as possible (about 8000 to 10,000 revolutions per minute). The red cells collect at the bottom of the tube and the relative volume occupied by them is read directly from the graduations on the tube. Although very simple, this instrument is not as accurate as the two instruments to be described, for which, on the other hand, is required an electrical centrifuge capable of running for at least 15 minutes.

Van Allen Hematocrit.—This instrument (Fig. 21) is now generally employed when only very small quantities of blood are available. Blood is drawn by suction to the upper mark on the stem of the tube and isotonic sodium oxalate solution (1.4 per cent) is next drawn up until the bulb above is about half full. The tube is then closed by means of the special spring sealing clip supplied and centrifugalized at 2,500 revolutions or more per minute until no further decrease in the volume of packed red cells takes place (about 30 minutes). The height of the column of packed red cells represents the relative volume of the blood which is made up by its red corpuscles. In our experience this instrument has not proved to be very accurate.

Wintrobe Hematocrit (Fig. 22).—Where somewhat larger quantities of blood are available this instrument is to be preferred since its accuracy is quite high, the probable error being no greater than 1 per cent. The instrument is a narrow glass tube about 10.5 cm. in length, of even bore and with a flat bottom. A centimeter-millimeter scale, commencing at the level of the inside bottom of the

hematocrit, is etched on the glass. Blood from an arm vein is collected as already described, coagulation being prevented by the use of potassium oxalate in the quantity already mentioned (p. 770). The hematocrit is filled to the 10 mark by means of a special pipet. A little less than 1 c.c. of blood is required. In order to prevent evaporation of plasma during centrifugation, the hematocrit is stoppered by means of a rubber cork. Centrifugation at 3,000 revolutions per minute, usually for 15 minutes and rarely for longer than 30 minutes, is necessary to secure complete packing. The time required is readily determined for any centrifuge by repeated centrifugation for different lengths of time until no further decrease in the volume of packed red cells is noted. If



FIG. 20.—DALAND HEMATOCRIT.

the tube has been filled exactly to the 10 mark the relative volume of packed red cells may be read directly from the graduations on the tube. If the upper level of the plasma is not at 10, the volume per cent of packed red cells may be calculated by dividing the height of the column of packed red cells by the total height of the column of cells and plasma and multiplying the result by 100. A correction for shrinkage in volume resulting from the use of potassium oxalate as the anticoagulant must always be made. When 10 mg. of oxalate are used for 5 c.c. of blood, a shrinkage of 5 or 6 per cent in the volume of packed red cells results. If the blood examined contains a large number of leukocytes or platelets, and particularly in leukemia, the blood should be permitted to remain in the hematocrit for some time before centrifugation is carried out. If this is done the red cells will settle to the bottom more quickly than the platelets or leukocytes and subsequent centrifugalization will result in a clear and quite accurate separation of the corpuscular elements of the blood. Unless this precaution is observed when examining bloods in which excessive numbers of leukocytes and platelets are present, the upper layer of packed cells

will consist of a mixture of red and white corpuscles which is sufficiently great to introduce an appreciable error in the readings.

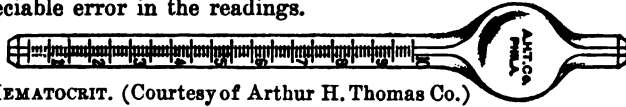


FIG. 21.—VAN ALLEN HEMATOCRIT. (Courtesy of Arthur H. Thomas Co.)



FIG. 22.—WINTROBE HEMATOCRIT. (Two-thirds actual size.)

VALUE OF THE HEMATOCRIT IN HEMATOLOGICAL STUDIES.—The determination of the volume of packed red cells in a sample of blood is of value in affording a macroscopic, quantitative conception of the cellular content of the sample as well as in permitting the calculation of the mean volume of the red cells (see below). The value of the information derived from the calculation of the color index depends in a very large measure on the fact that in most types of anemia the hemoglobin content of the red corpuscles varies directly with its volume, and therefore by the determination of this hemoglobin content (color index or mean corpuscular hemoglobin) a conception of its size is gained. Such information is of distinct value in the recognition of macrocytic types of anemia such as pernicious anemia and will probably prove useful in the differentiation of other types of anemia. Since hemoglobin estimations are usually performed with notorious inaccuracy whereas the determination of the volume of packed red cells can be readily and accurately carried out, hematocrit determinations are at present of particular value. Furthermore, where it is possible to have both accurate hemoglobin as well as accurate hematocrit determinations, the hematocrit is again of value in making possible the calculation of mean corpuscular hemoglobin concentration or saturation index.

DETERMINATION OF THE SIZE AND HEMOGLOBIN CONTENT OF THE RED CORPUSCLE

The Determination of the Size of the Red Corpuscles.—(a) **THE MEASUREMENT OF CELL DIAMETER.**—A number of methods, such as those of Price-Jones and of Ponder and Millar, have been employed for the measurement of cell diameter which, although relatively accurate, are too laborious and require the use of too much special apparatus to be of any value in clinical work. There is available for this purpose, however, a micrometer ocular (Fig. 23) by means of which diameter measurements can be very easily made, although such measurements are not as accurate as are those derived by the use of more complex methods. The special ocular can be placed into the draw tube of any microscope. As one looks into the instrument a vertical scale which overlies any object brought into focus can be seen. The measurements on this scale can be calibrated by means of a slide micrometer for the particular tube length and lenses employed. By means of a micrometer screw and calibrated drumhead, the vertical scale can be moved from side to side and measurements can therefore be made in a horizontal as well as in a vertical direction.

A thin portion of a stained smear is brought into view and the diameter of the cells is measured. The horizontal and vertical diameter of all cells may be measured and the mean of these taken as their diameter, or, more simply, the vertical diameter of all round cells which come under the micrometer scale as the slide is moved in a vertical direction can be taken as an index of their size. The former method is of course the more accurate, and with both methods the greater the number of cells measured the greater will be the value of the result. Price-Jones cautions that care and uniformity in the method of staining must

be observed. It is important to determine the normal value for the technic one employs.

Instead of the micrometer ocular above mentioned, a micrometer disc of glass marked with a scale one division of which equals (approximately) one micron, may be purchased and placed inside the ocular of any microscope. The scale on this disc may be calibrated for the tube length and lenses employed by means of a slide micrometer, or a hemocytometer may be used for this purpose, the smallest squares of the latter being 50 microns to the side. With some microscopes it is possible to adjust the tube length so that the divisions of the micrometer eyepiece fit those of the slide micrometer or hemocytometer. If this is not possible a correction factor must be determined.



FIG. 23.—MICROMETER OCULAR
(Courtesy of Leitz Co.)

Pijper, Millar, Emmons, and Eve have described instruments for the measurement of cell diameter which are based on the principle that when parallel light rays are passed through a blood smear placed in front of a convex lens, concentric spectrums are produced, the size and character of which depend on the size and shape of the cells. Although the measurements by this method are readily performed they yield average figures only and therefore afford no information which cannot be derived as readily and more accurately from the calculation of mean corpuscular volume (see below).

(b) THE MEASUREMENT OF THE VOLUME OF THE RED CORPUSCLE.—(1) No simple method of measuring directly the volume of the red corpuscles is as yet available, but the mean volume of the corpuscles of any sample may be very easily calculated when the red cell count and the volume of packed red cells, as determined by means of one of the hematocrits before described, are known. The volume index of Capps expresses the mean volume of the red corpuscles of any sample of blood in relation to an arbitrary normal. The volume index is calculated from the formula.

$$\text{Volume Index} = \frac{\text{Volume of packed red cells per cent}}{\text{Number of red cells per cent}}$$

The arbitrary normal employed as 100 per cent red corpuscles is 5,000,000 per c.mm. The normal volume of packed red corpuscles which should be used as the equivalent of 100 per cent packed red cells is 42.4 c.c. per 100 c.c. of blood (see Chapter I, this section).

The method of calculation is best described by the citation of an example. Let it be supposed that a sample of blood contains 4,100,000 red cells per c.mm. and the volume of packed red cells, as determined by the hematocrit, is 31 c.c. of cells per 100 c.c. of blood. Then the volume of packed red cells in per cent is $(31/42.4) \times 100$ or $31 \times \text{the factor } 2.36$ ($100 \div 42.4$) = 73 per cent. The number of red cells, in per cent, is $(4.1/5) \times 100$ or $4.1 \times \text{the factor } 20$ = 82 per cent. Then the volume index of this sample is $(73/82) = 0.89$.

(2) A more simple calculation which does not require the use of an arbitrary

TABLE I
NORMAL ERYTHROCYTE VALUES

	Normal Average		Normal Minimum		Normal Maximum	
	Male	Female	Male	Female	Male	Female
Red blood corpuscles (in millions per c.mm.)	5.5	4.78	5.0	4.4	6.5	5.3
Hemoglobin (in grams per 100 c.c. blood)	16.2	13.9	14.5	12.5	18.5	15.0
Relative volume of packed red cells, (c.c. per 100 c.c. blood)	46.0	41.0	40.0	37.0	50.0	45.0
Mean Corpuscular Volume (in cubic microns)	85		75		95	
Mean Corpuscular Hemoglobin (in micromicrograms)	28.5		26.5		31.5	
Mean Corpuscular Hemoglobin Concentration (in per cent)	35		33		39	

TABLE II
RELATIVE AND ABSOLUTE NORMAL LEUKOCYTE COUNTS (PER CU. MM.)

TYPE OF CELL	PERCENT	ABSOLUTE NUMBER		
		Average	Minimum	Maximum
Total Leukocytes		7,000	5,000	10,000
Myelocytes	0	0	0	0
Juvenile Neutrophils	4-8%	400	200	700
Segmented Neutrophils	56-62%	4,200	2,800	5,800
Eosinophils	1-3%	200	50	300
Basophils	0-0.75%	35	15	75
Lymphocytes	20-30%	2,000	1,000	3,000
Monocytes	4-8%	450	300	600

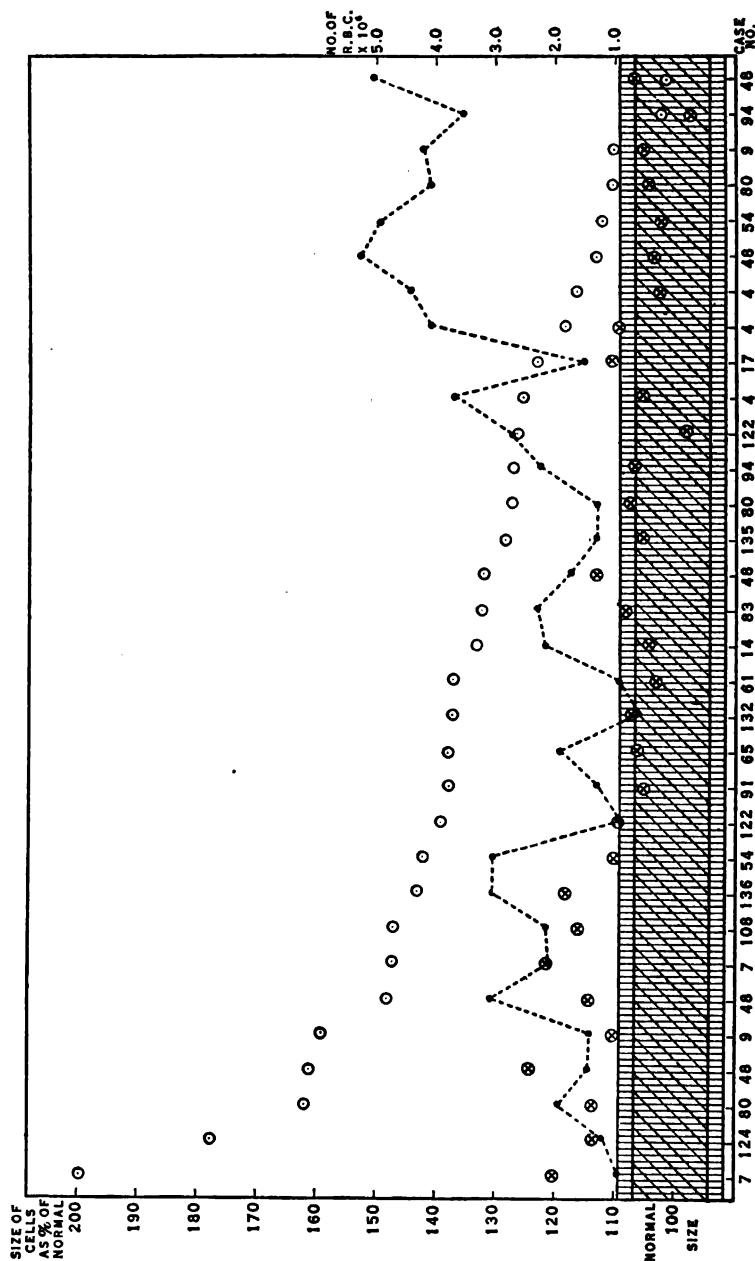


FIG. 24.—The comparative value of mean corpuscular volume determinations and mean cell diameter values in the diagnosis of macrocytosis. Thirty-two determinations in 14 cases of pernicious anemia and 5 cases of sprue in all stages of severity. The values for mean corpuscular volume and mean cell diameter are expressed as per cent of normal, 82 cu. μ being taken as the mean normal corpuscular volume, and 7.94 the mean normal diameter. The corpuscular volume values have been arranged in order of magnitude and the corresponding cell diameter and red cell count are placed in the corresponding vertical position. ○ is the corpuscular volume, ⊙ the cell diameter, and ● the red cell count for each patient. The larger vertically shaded portion denotes the normal range of variation in corpuscular volume and the smaller diagonally shaded area the normal range of cell diameter as indicated by the coefficients of variation for these values, 9 per cent and 6.3 per cent respectively. In most instances the mean cell diameter values are within the normal range of variation or are little in excess of normal. The mean corpuscular volume values were all significantly above normal excepting when the blood count was normal or nearly so. (Wintrobe, Am. J. Med. Sc.).

trarily fixed normal is that by which *mean corpuscular volume* is calculated. This is determined by dividing the volume of packed red cells, expressed in cubic centimeters per 1000 c.c. of blood, by the number of red cells expressed in millions per c.mm. The result expresses mean corpuscular volume in cubic microns.

For the example used to illustrate the calculation of volume index, namely, a sample of blood which contains 4,100,000 red cells per c.mm. and 31 c.c. of packed red cells per 100 c.c. of blood, the mean corpuscular volume is $310 \div 4.1 = 76$ cubic microns.

As an index of the mean size of cells, volume determinations are undoubtedly of more value than are diameter measurements for, by the estimation of the former, mean variations in all dimensions are included (*vide* Fig. 24). The particular usefulness of diameter measurements is to be found in the recording of variations in the size of individual cells. The significance of alterations in the size of cells has already been briefly discussed in Chapter I and will be further considered in subsequent chapters.

(c) THE ESTIMATION OF MEAN CORPUSCULAR THICKNESS.—Where the mean cell diameter and mean corpuscular volume are known, the mean corpuscular thickness may be calculated from the formula, $T = C.V. / (D/2)^2$ where T = mean corpuscular thickness, $C.V.$, mean corpuscular volume and D , mean cell diameter.

The Estimation of the Hemoglobin Content of the Red Corpuscle.—(a) The hemoglobin content of the red corpuscle can be measured only indirectly. The *color index* measures the average amount of hemoglobin contained in the red corpuscles of the sample of blood in proportion to an arbitrarily fixed normal. It is calculated from the formula,

$$\text{Color Index} = \frac{\text{Hemoglobin per cent}}{\text{Number of red cells per cent.}}$$

The percentage of hemoglobin is read directly from the scale of a hemoglobinometer, or, if the amount of hemoglobin has been determined in grams, the percentage may be calculated on the basis of 14.5 gm. of hemoglobin per 100 c.c. of blood as the equivalent of 100 per cent hemoglobin. In the calculation of color index 5,000,000 per c.mm. is the value used as 100 per cent red cells.

Let it be supposed that the sample of blood already cited contained 10.5 gm. of hemoglobin per 100 c.c. of blood. This is equivalent to $(10.5/14.5) \times 100$, or $10.5 \times \text{the factor } 6.9 (100 \div 14.5) = 72$ per cent hemoglobin. The number of red cells in this sample was 4,100,000, or 82 per cent. Then the color index is $(72/82) = 0.88$.

(b) The amount of hemoglobin contained in the average red corpuscle of any sample of blood may also be calculated directly without comparison to an arbitrarily fixed normal. *Mean corpuscular hemoglobin* is calculated by dividing the amount of hemoglobin, expressed in grams per 1000 c.c. of blood, by the number of red cells, expressed in millions per c.mm. The result expresses in micromicrograms* the amount of hemoglobin contained in the average red corpuscle of the sample. Thus, for the example just cited, the mean corpuscular hemoglobin is $105 \div 4.1 = 25.6$. Normal values have already been given in Chapter I (p. 743).

(c) The hemoglobin content of the red corpuscle, expressed in proportion to its volume and in relation to an arbitrary normal, is indicated by the *saturation index* (Haden). This is calculated from the formula,

$$\text{Saturation Index} = \frac{\text{Hemoglobin per cent}}{\text{Volume of packed red cells per cent.}}$$

In the sample already cited, there were 10.5 gm. of hemoglobin, or 72 per cent, and 31 c.c. of packed red corpuscles, or 73 per cent. The saturation index is therefore $72/73$, or 0.99.

(d) The proportion of hemoglobin contained in the average red corpuscle of any sample of blood may also be calculated directly without comparison to any arbitrarily fixed normal by dividing the amount of hemoglobin in the sample, as expressed in grams per 100 c.c., by the volume of packed red cells, expressed

* A micromicrogram is the millionth of a millionth part of a gram (grams $\times 10^{-12}$) and is abbreviated by the Greek letters gamma $\gamma\gamma$.

in cubic centimeters per 100 c.c. of blood, and multiplying the result by 100. The resulting value expresses in per cent the proportion of hemoglobin in the average red corpuscle and is termed *mean corpuscular hemoglobin concentration*.* The mean corpuscular hemoglobin concentration for the example cited is $(10.5/31) \times 100 = 34$ per cent.

RELATIVE VALUE OF THE INDEXES AND DIRECT CALCULATIONS OF THE VOLUME AND HEMOGLOBIN CONTENT OF THE RED CORPUSCLE.—The chief merit of the indexes used in hematology, namely, the volume index, the color index and the saturation index, is that they express the mean volume and hemoglobin content of the red corpuscle in terms of normal. This, however, is likewise their chief disadvantage since they require the fixation of arbitrary values for normal. Direct calculations of the mean volume and hemoglobin content of the red corpuscle, on the other hand, require no such arbitrarily fixed values, and furthermore, since the results are expressed directly in cubic microns, micromicrograms or per cent, their meaning is more readily grasped and the significance of variations more easily appreciated. For a further discussion of this subject the reader is referred to the papers of Wintrobe.

THE MICROSCOPIC EXAMINATIONS

Care and Preparation of Slides and Cover-glasses.—Scrupulous care in the cleansing of glassware is necessary to obtain the best results. All material should be of the best sort. Both the slides and cover-glasses should be thin.† Seven-eighth inch (22 mm.) square cover-glasses are superior to the round. When received from the dealer they should be thoroughly washed in soap or bon ami and hot water. If preferred they may be placed in concentrated nitric acid or a mixture of sulphuric acid and potassium bichromate‡ for several hours and then thoroughly washed in running water, distilled water, and finally immersed in 95 per cent alcohol. Glassware may be kept in alcohol and dried before use or it may be dried at once with a piece of old linen or Japanese lens paper and stored in dust-proof receptacles.

Examination of the Fresh Blood.—The examination of fresh blood affords a useful quick means of survey. A freely flowing drop of blood is touched with the middle of a clean cover-glass, held by means of a pair of flat bladed forceps, or, if preferred, by the fingers in such a manner that only the edges of the glass are touched. The drop should be no larger than a pinhead. The cover-slip is immediately inverted on a clean glass slide. If the glassware is clean the blood will spread out evenly under the weight of the cover-slip. Pressure should not be made. The edges of the cover-glass are rimmed with vaseline and the specimen is examined with the oil immersion lens.

This procedure is valuable for the observation of the size, shape and color of the red corpuscles and is necessary for the detection of sickle cell formation. Rouleaux formation may be observed and increase or decrease of fibrin may be roughly gauged after the specimen has stood for 10 to 15 minutes. A rough estimate of the number of leukocytes can be gained and their motility observed. With the aid of dark field illumination the method is valuable for the detection and observation of parasites. By the staining of such preparations with neutral red or Janus green by Pappenheim's method (supravital staining) and the examination of the slides on a warm stage, much valuable information concerning living cells may be gained. The reader is referred to the papers of Sabin and her associates for details of this work.

Making the Blood Smear.—To make a good blood smear cover-glasses or slides may be used, but these must be absolutely clean and dry and the utmost care must be observed to make no pressure such as may result in deformity or fracture of the blood cells. If *two cover-glasses* are used (Fig. 25) a small drop of blood at the point of puncture should be lightly touched by one, the other placed quickly and gently upon it, allowed to remain an instant to permit the spread of the blood between the two surfaces, and then separation of the two effected

* This constant is useful rather than accurate in a physical sense since it is assumed that hemoglobin is contained in the red corpuscle in the form of an aqueous solution.

† Number 2 thickness (0.17 to 0.25 mm.) or preferably number 1 (0.13 to 0.17 mm.).

‡ Potassium bichromate 100 gm., sulphuric acid 250 c.c., water 750 c.c.

by a sliding (not a lifting) movement, all downward pressure being avoided. The cover-slips should be placed on one another in such a manner that the drop is spread without causing bubbles. The drop is allowed to spread until it has almost stopped spreading. The cover-slips should be held at adjacent corners with the thumb and forefinger of each hand and placed on one another at such an angle that in sliding them apart they may be held by the fingers in the same

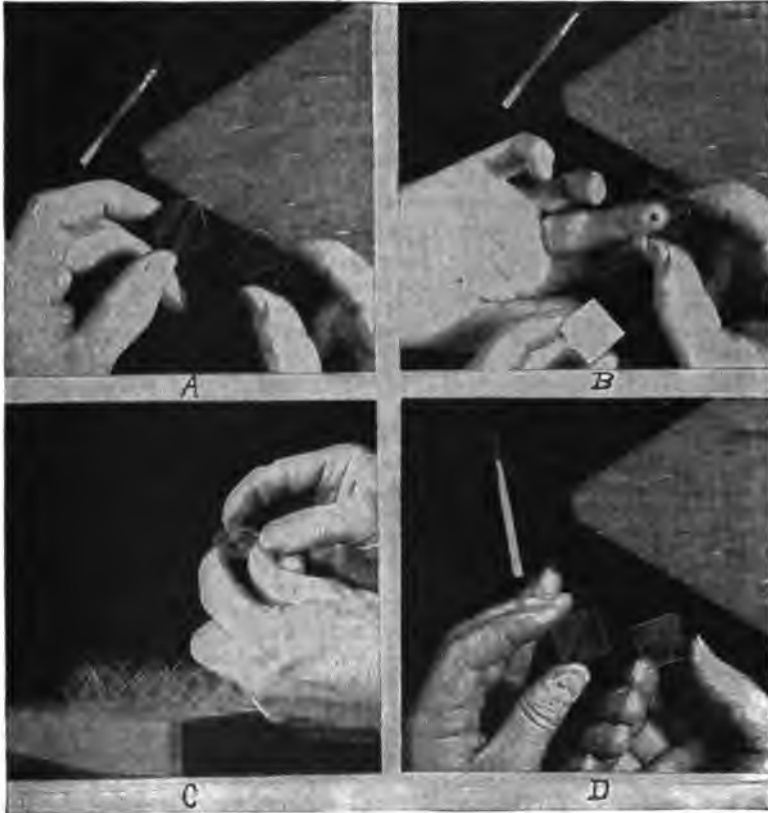


FIG. 25.—THE PREPARATION OF BLOOD FILMS BY THE COVER-GLASS METHOD. (Haden, Clinical Laboratory Methods, C. V. Mosby Co.)

manner. The glass surface upon which the spread is to be made should never be allowed to touch the skin of the patient.

For making smears on slides a drop of blood is taken up towards the end of one slide which is then held drop upward between two fingers and steadied by a third finger of the left hand (Fig. 26). The drop of blood should be at the end of the slide which is closer to the right hand. The short edge of another slide is then allowed to rest upon this slide just in front of the drop of blood at an angle of approximately 30° . The spreader slide is pulled back to the drop which is allowed to spread outwards to both edges. All the blood should be behind the sharp edge of the end of the spreader slide which is then pushed with a rather quick but steady movement toward the end of the smear slide. The smear will be thin or thick according as the movement is slow or rapid. A good spread should be smooth, homogeneous and without serrations, have even edges and should occupy approximately the middle third of the slide. The cells should be evenly distributed throughout large areas and should not look smeary or thick to the eye. The smear is allowed to dry in the air.

Fixation of Dried Preparation.—Fixation is secured by heating at 120° to 125° C. for a few minutes or by passing the slides through a small flame three or four times; by boiling one minute in absolute alcohol; or by immersion for one minute in a 1 per cent alcoholic solution of formalin. Wright's stain and Wilson's stain, however, consist of a solution of the respective dyes in absolute

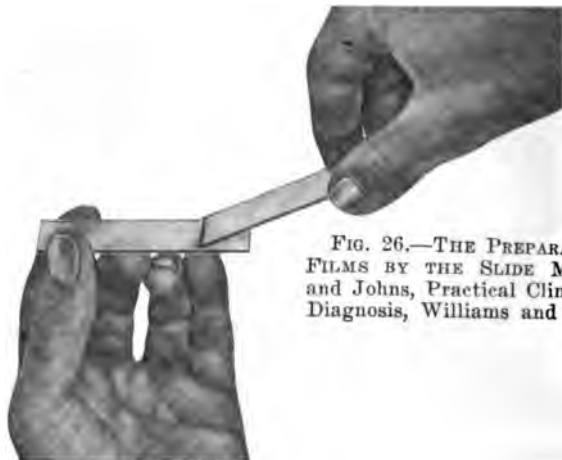


FIG. 26.—THE PREPARATION OF BLOOD FILMS BY THE SLIDE METHOD. (Bass and Johns, Practical Clinical Laboratory Diagnosis, Williams and Wilkins Co.)

methyl alcohol, and fixation is therefore brought about in the first minute when the undiluted stain is applied to the smear.

Staining of the Blood Smear.—Modern staining methods depend upon the selective affinity shown by the different constituents of the cellular elements of the blood for certain aniline dyes. These are divided into three groups: (a) basic, (b) acid and (c) neutral. The basic dyes such as methylene blue, hematoxylin or methyl-violet (chromatin stains), act chiefly upon the nuclei. Acid dyes, such as eosin, orange G. or acid fuchsin, are protoplasm stains. In the so-called neutral or polychrome dyes which are formed from the mixture of acid and basic dyes, the staining principles of the original components are preserved and also new staining properties which depend on the component dye are formed. Neutral dyes color beautifully the "neutrophil" granules of the leukocytes.

STAINING SOLUTIONS.—Ehrlich's triacid stain has now been supplanted by a number of more useful stains such as Jenner's stain or one of the modifications of the Romanowsky method such as that of Wright, Wilson or Leishman. Wright's stain is most generally used and the description of cells in this section refers, unless otherwise stated, to their appearance when stained by this method.

Wright's stain is an eosin-methylene blue mixture. The student or practitioner had best purchase the "soloid" tablets* or procure a solution ready-made through some drug supply house, as the formula† is somewhat complex. The stain should be tightly corked to prevent precipitation.

TECHNIC OF STAINING.—(1) The dried but unfixed smear is completely covered with stain for one minute. (2) Distilled water is added to the stain on the

* The "soloid" tablets of Arthur H. Thomas Company offer a ready method of making up fresh stain. One soloid is triturated with 10 c.c. (2.71 fluidrams) of pure methyl alcohol, the dissolved stain decanted and the undissolved stain again extracted with another 10 c.c. of alcohol. This process is repeated a third time so that 30 c.c. (1 fluid ounce) in all are used. The stain should be passed through a filter.

† *Formula.*—(a) Make a 0.5 per cent aqueous solution of sodium carbonate, place in Erlenmeyer plaque, add 1 gram of methylene blue (B.X. or "medically pure") per 100 c.c. of the solution; place in steam sterilizer for an hour. (b) After cooling, add while stirring with glass rod, a 1-1000 aqueous solution of water-soluble yellowish eosin until the color of the original mixture changes to purple and presents a lustrous yellowish scum upon its surface. (About 1/5 as much eosin solution as methylene-blue solution will be found necessary.) (c) Collect this scum by filtration, dry it and with it saturate methyl alcohol (100 c.c.—3.38 fluid ounces—of the latter will dissolve about 0.3 gram of the dry precipitate). (d) Filter and add 25 per cent of methyl alcohol. The stain is now ready for use and, if kept tightly corked, should neither precipitate nor show impairment though kept for a long period.

smear drop by drop until a greenish metallic scum appears and the margins show a reddish tint. The quantity of water added should be about the same as the amount of dye used, this being conveniently gauged by counting the number of drops. In adding the distilled water care should be taken that the solution does not run over the edges of the slide (or cover-slip). (3) After three minutes the stain is washed off with water, leaving a purplish specimen which is washed until the film is yellowish or pink. Washing should be commenced while the stain is still on the slide as otherwise a scum which cannot be removed by subsequent washing tends to settle on the film. (4) The slide is allowed to stand on end to dry. This is preferable to drying between filter papers. (5) Finally the preparation is mounted in Canada balsam.

It is important to keep the film well covered with stain throughout the staining process. Evaporation, which may take place very rapidly in a dry atmosphere, will cause the stain to precipitate on the film.

Results.—In a successful stain the film will appear pink to the naked eye, the erythrocytes will be pink, the nuclei of the leukocytes purplish blue, neutrophil granules violet-pink or lilac, eosinophil granules red, all granules will be clearly shown and the basi- and oxy-chromatin of nuclei clearly differentiated. If the stain is too blue, this may be due to overstaining or to the use of too alkaline a preparation. Some pathologic bloods will be stained too blue by a technic which is satisfactory for normal blood. For overstaining, less stain and more diluent should be used, or the time of staining may be decreased and the time of washing increased. Haden suggests the use of a buffer † to counteract an excess of alkali in the stain. The amount necessary can be determined only by trial but 3 drops of buffer to 8–10 drops of distilled water will usually be satisfactory. Haden suggests that if the stain is very alkaline the buffer be used in place of water. More simply, a drop of weak acetic acid may be added to the stain if it is too alkaline or a drop or two of ammonia water is employed when it is too acid.

The Differential Leukocyte Count.—It is advisable to follow a definite routine in carrying out the differential leukocyte count. The oil immersion lens is essential for the careful differentiation of the cells. A mechanical stage is invaluable. The most accurate count is obtained by examining *all* the leukocytes in *both* smears of a cover-slip preparation. This, however, is time-consuming and may necessitate the examination of several thousand cells. Even when this

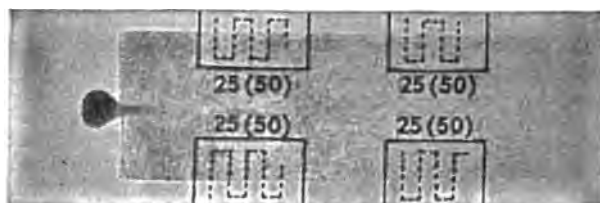


FIG. 27.—SCHILLING'S "FOUR FIELD MEANDER" METHOD FOR DIFFERENTIAL LEUKOCYTE COUNTING. (Schilling and Gradwohl, *The Blood Picture*, C. V. Mosby Co.)

is not done films on cover-slips are preferable because when drawn or pulled on slides the larger leukocytes tend to accumulate at the margins while the smaller cells (lymphocytes) are distributed in the central portions of the films. In order to overcome these disadvantages Schilling recommends the examination of slides by a "four field meander" technic (Fig. 27). Four fields of the slide are examined, one-fourth of the total number of leukocytes which it is desired to count being examined in each of these areas. In each field the preparation is moved to the side for several fields of vision, then out to the edge of the smear, then to the side and inward for a short distance, and so on until the required number of cells is counted. Slides are perfectly satisfactory for studying

† Haden's phosphate buffer solution is made up as follows: recrystallized primary (monobasic) potassium phosphate 6.63 gm., anhydrous secondary (dibasic) sodium phosphate (Merck) 2.56 gm., distilled water to make 1000 c.c. The solution should have a pH of 6.4.

qualitative changes in the white corpuscles and are even preferable for the study of red cells and for a search for parasites. The classification of leukocytes has already been discussed in Chapter I, this section.

Peroxidase Staining.—While Wright's stain is satisfactory for most work, much remains to be desired as regards the differentiation of myeloblasts from lymphoblasts, myelocytes and metamyelocytes from monocytes, and particularly in the acute leukemias, myeloid cells and monocytes from lymphocytes. The peroxidase method of staining is used to facilitate the differentiation of cells of the granulocytic series from lymphocytes. The method depends on the oxidation of benzidine by hydrogen peroxide and a consequent deposition of pigment which is initiated by and occurs as the result of the presence of oxidizing ferment in myeloid cells.

Goodpasture's technic, as modified by Beacom, is most generally employed. The blood film, made in the usual manner, is covered with the stain* for 1 minute. An equal amount of a freshly made 1:200 dilution of hydrogen peroxide is then added and allowed to stand 3 or 4 minutes. The film is next washed and allowed to dry. The peroxide solution is prepared by adding 2 drops of fresh hydrogen peroxide to 15 c.c. of distilled water.

By this method nuclei appear clear red, cytoplasm pink, and red cells a smooth buff color. Neutrophilic granules of myelocytes or polymorphonuclear leukocytes are stained deep blue and are well defined. Eosinophilic granules are dark blue but basophilic granules are not shown. No granules are seen in the lymphocytes. Granules which are fewer in number and less well defined than in the myeloid series of cells are seen in most monocytes. A positive peroxidase reaction is of great value since lymphocytes are thereby definitely ruled out. A negative reaction is of less value because the very primitive cells of the myeloid series, the myeloblasts, do not give a positive reaction.

An alternative technic for peroxidase staining is that recommended by Graham. A few crystals (as much as can be taken up on a small knife blade) of benzidine are dissolved in 10 c.c. of 40 per cent alcohol, and 8 c.c. of commercial (3 per cent) hydrogen peroxide are added. The blood smear is fixed with a solution of 9 parts of 95 per cent alcohol and 1 part of freshly prepared formaldehyde solution (40 per cent gas). The fixative is allowed to act for 1 to 2 minutes. The film is then washed and covered with the benzidine solution already described, which is permitted to remain for 5 to 10 minutes. The film is again washed and stained with Loeffler's methylene blue for 30 seconds.

Although the technic of staining by the peroxidase method appears simple, failure to stain the granules of the myeloid cells is more common than success. This is most often due to the use of weak or insufficient hydrogen peroxide but may also be the result of insufficient time of staining or excessive dilution with water. Sometimes it may be found that there is insufficient benzidine in the stain. At other times cells so deeply stained that the granules cannot be made out may be encountered if too much peroxide has been used or the preparation has been overstained.

Our own experience has been that, even when these precautions have been observed, failure to stain the granules of the myeloid cells has resulted. We have found to be very much less "tricky" the "*copper*" peroxidase method of Sato and Sekiya: Solution A † is applied to a fresh dry blood smear for 30 to 60 seconds. This is then poured off ‡ and Solution B is applied for 2 minutes. This is poured off and the counterstain applied for 2 minutes. The smear is

* Goodpasture's peroxidase stain, as modified by Beacom, consists of the following: Alcohol 100 c.c., sodium nitroprusside 0.05 gm., benzidine C.P. (Harmer) 0.05 gm., basic fuchsin 0.05 gm. The nitroprusside is dissolved in 1 to 2 c.c. of water, mixed with alcohol and then the other ingredients are added. This stain will keep for 8 months.

† Sato and Sekiya, Solution A: Copper sulphate solution, 0.5 per cent; Solution B: Rub 0.2 gm. of benzidin (benzidin, puriss. Merck or benzidin, base Merck) with a few drops of water in a mortar. To this are added 200 c.c. of water at room temperature and a saturated solution of benzidin is thus prepared. The preparation is filtered and 4 drops of hydrogen peroxide (3 per cent) are added. If this preparation is kept in the dark when not in use, it will last a year. It may be tested by mixing solutions A and B in a test tube. If this mixture does not become blue, the reagents are at fault. Most often the benzidin solution (Solution B) is not saturated.

‡ We have found that if Solution A is washed off, blue precipitates on the smear are avoided.

then washed thoroughly and dried. As counterstain safranine (1 per cent aqueous solution) or carbol fuchsin (one part in five) may be used. By this method the cytoplasm of the myeloid leukocytes is stained blue and the peroxidase-positive granules bluish-green with the eosinophil and basophil granules intensively blue; monocytes are most faintly stained and their granules appear small though distinctly blue. Lymphoid elements show no trace of blue or green but appear red. Red cells and platelets remain unstained either by peroxidase or by counterstain except when carbol fuchsin is used.

The Enumeration of Reticulocytes.—Perhaps the simplest method of making a rough estimate of the proportion of young, reticulated red corpuscles consists in placing a drop of saturated aqueous solution of brilliant cresyl blue on the finger or ear lobe, puncturing through this and making blood films from the resulting mixture of stain and blood. By another method slides are first prepared by allowing a thin, even layer of a saturated alcoholic solution of brilliant cresyl blue to dry on them. Blood smears are then made on the slides so prepared.

We have found the following method (Haden) most satisfactory: Five c.c. of a saturated aqueous solution of brilliant cresyl blue are mixed with 1 c.c. of 2 per cent sodium oxalate solution and filtered. One or two drops of this mixture are drawn into each of several capillary pipets, the excess is blown out, and the pipets are placed in an incubator until the stain has evaporated to dryness. These preparations will keep indefinitely.

The finger is punctured so as to get a free flow of blood. A good-sized drop of blood is drawn up into one of the capillary pipets containing the stain. After two or three minutes, the blood is blown out on to cover-slips or slides and blood films are made in the usual manner. If desired, the slides may be counterstained with Wright's stain. The number of these cells in proportion to adult red cells is determined. A piece of cardboard in which a perforation about $\frac{1}{4}$ inch square has been made should be placed in the eyepiece to decrease the size of the field and thus facilitate counting, or an Ehrlich reducing ocular may be used for this purpose.

A somewhat more accurate method has been described by Friedlander and Wiedemer. By this method blood is diluted with a special solution of brilliant cresyl blue.* In order to ensure satisfactory staining of the reticulocytes this mixture is allowed to stand for 30 minutes, and preferably much longer. The pipet is then shaken once more and a count of reticulated red corpuscles is made in the blood counting chamber. These writers recommend the use of a special pipet which permits a dilution of 1:40 and a special microscope objective which gives a magnification higher than the ordinary 4 mm. lens. These are, however, not essential. Reticulocytes can be made out by means of the 4 mm. objective. By drawing the blood to the second graduation of a white cell pipet (the 0.2 mark) and diluent to the "11" mark, a dilution of 1:50 is made. The count is carried out in the squares used for the white cell count and the result is multiplied by 125 to give the value per c.mm. An alternative method consists in the dilution of the blood with the special cresyl blue solution in a red cell pipet as for a red cell count. This method has the advantage that a red cell count may be made at the same time but the accuracy of the reticulocyte count is not as great since the blood dilution is 1:200 instead of 1:40 or 1:50. This disadvantage may be partially obviated by enumerating the reticulocytes seen in all 25 of the squares used for the red cell count.

EXAMINATIONS CONCERNED WITH COAGULATION

The Enumeration of the Blood Platelets.—*Indirect Methods.*—The simplest method consists in the enumeration of the number of platelets seen while counting a certain number of leukocytes or red corpuscles in a smear. The relative numbers of platelets and leukocytes (or red cells) being thus determined, the total number of platelets per cubic millimeter is readily calculated if the number of white or red corpuscles is known. The smear may be taken in the usual manner

* *Reticulocyte Solution:* Stock solution I: 1 per cent aqueous solution of brilliant cresyl blue; stock solution II: sodium chloride 0.6 gm., potassium oxalate 0.2 gm., distilled water to 100 c.c. These stock solutions keep indefinitely in a cool place. When needed for use 1 part of solution I is added to 4 parts of solution II. This third solution will keep about one week and may require filtering.

and stained with Wright's stain or some diluting fluid may be first placed on the skin. Fonio's method consists in placing a drop of 14 per cent aqueous solution of magnesium sulphate on the skin and puncturing the finger through this. The blood which should well up freely becomes diluted and clumping of the platelets is prevented. A smear is made from this diluted blood and is stained in the usual manner. Overstaining may be necessary to make the platelets sufficiently clear.

Direct Methods.—Direct methods by means of which the blood platelets are enumerated in a counting chamber are somewhat more accurate than the methods just described. A Thoma red cell pipet is used. In order to prevent the platelets from sticking to the dry glass, the pipet is first filled with diluting fluid which is then immediately expelled, leaving a film inside the pipet. It is well to place a thin coat of vaseline on the finger in order to ensure smoothness of surface. The finger is punctured through this, the first drop is wiped away, and from the second drop the blood is drawn to exactly the 0.5 mark and diluting fluid is drawn to the 101 mark. These steps should be carried out quickly as exposure to air causes the platelets to agglutinate. The count is carried out in a counting chamber in the same manner as is the red cell count, all the platelets seen in 5 groups of 16 small squares (new Neubauer ruling) being counted and this number multiplied by 10,000 to give the number per c.mm. Ten minutes should be allowed for the platelets to settle before the count is made. As diluting fluid the one recommended by Rees and Ecker* is most often employed. The platelets appear as round, over or elongated lilac-colored bodies. When the fine adjustment of the microscope is focused up and down, they may be seen as highly refractile, glistening bodies one-fifth to one-half the diameter of the red corpuscles. They may be seen singly or in groups. The nuclei of the leukocytes are also stained, but these cells are readily distinguished. The red corpuscles are preserved and may be counted in the same specimen. It is very important that the counting chamber and pipet be scrupulously clean.†

None of the methods for enumerating blood platelets are entirely satisfactory. The properties of platelets being such that they very readily agglutinate or adhere to any foreign object and immediately disintegrate, it has not been possible as yet to devise an entirely satisfactory technic. For a review of this subject the reader is referred to the recent paper by Olef.

Van Allen has devised a thrombocytocrit for the separation of the platelets by centrifugation. The method should prove of value in special cases.

Estimation of Bleeding Time (Duke).—A moderately deep cut is made in the finger or ear lobe with a sharp blood lancet. The cut should be sufficiently deep to cause the blood to ooze without any pressure. At intervals of one-half minute the drop of blood exuding is removed by means of a blotter or filter paper, but the skin should not be touched. The time required for the bleeding to cease spontaneously is noted.

Normal bleeding time by this method is 1 to 3 minutes. Bleeding time greater than 10 minutes may be considered prolonged. Bleeding time is prolonged notably in conditions in which the blood platelets are reduced in number as in purpura haemorrhagica. Duke also noted prolongation of the bleeding time in conditions in which the fibrinogen content of the blood is extremely low, as in chloroform and phosphorus poisoning.

Retraction Time of Blood Clot.—For the carrying out of this test 2 or 3 c.c. of blood are collected in a test tube. The blood is allowed to clot and is then separated from the sides of the tube by means of a fine wire. It is next placed in an incubator at 37° C. and observed for several days. Retraction of the blood clot normally commences in a few hours and is complete within 18 to 24 hours. In conditions in which blood platelets are reduced in number, such as purpura haemorrhagica, the clot which forms within the normal time does not retract.

Coagulation Time.—In determining coagulation time several important pre-

* The diluting fluid of Rees and Ecker consists of sodium citrate 3.8 gm., formaldehyde, 40 per cent solution, 0.2 c.c., brilliant cresyl blue 0.1 gm. and distilled water 100 c.c. It should be filtered before using.

† Another diluting fluid which is recommended is that of Pratt, which is made up of sodium metaphosphate (Merck) 2 gm., sodium chloride 0.9 gm. and distilled water 100 c.c. The solution should be centrifugated or filtered before using.

cautions must be observed, as otherwise the test will be valueless. It is important for the sake of comparison that blood be obtained by exactly the same technic each time. The same sort and size of vessel should be used and the same conditions of cleanliness and smoothness of instruments observed. Temperature conditions should be the same, since the coagulation time becomes prolonged or shortened as the temperature is lowered or raised. Finally, it is important that there be no traumatization or even squeezing of the source of blood since the exudation of tissue juice which is produced causes a decrease in the coagulation time.

Several methods for the determination of coagulation time in which blood is obtained by *skin puncture* are in use, but these cannot be recommended as being very reliable. In the simplest of these the finger is cleaned with alcohol and then coated with vaseline. A deep needle puncture is made so that the drop of blood will exude without pressure onto the vaselined surface. After 5 minutes and at intervals thereafter a needle which has been coated with vaseline is passed through the drop until the clot is caught upon it. The normal coagulation time by this method is 2 to 10 minutes.

For another generally used method, 5 or 6 capillary tubes having a lumen about the size of the lead in a pencil are required. These are filled from a large drop of blood which has exuded from a deep cut. At each one-half minute interval the glass of a pipet containing the blood is marked with a file and carefully broken. The appearance of a fibrin thread between the fragments as they are slowly separated is the end point. Normal coagulation time by this method is 3 to 7 minutes.

For more accurate determination of coagulation time *venipuncture* is necessary: *Howell's Method*.—An all-glass syringe to which a sharp hypodermic needle is attached is rinsed out with normal saline solution. This is ejected with the syringe held in a vertical position so that normal saline remains in the needle and in the space between the end of the plunger and the needle. This is done so that the blood will not come in contact with air which hastens coagulation. Two c.c. of blood are withdrawn from an arm vein. A tourniquet may be used. It is important that the vein be entered quickly and neatly, as otherwise tissue juice will enter the syringe and invalidate the result. The blood is placed in a vial 21 mm. in diameter and inclined from time to time in order to observe the state of fluidity. The end point is the moment when the clot is firm enough to permit inversion of the tube. Normal blood tested by this method coagulates usually in 20 to 40 minutes at room temperature.

The method of Lee and White is essentially similar, but 1 c.c. of blood is placed in a small Wassermann tube, about 8 mm. in diameter, which is thoroughly clean and has been rinsed out with normal salt solution. It is well to prepare several tubes in this way and place 1 c.c. of blood in each. While one or two of these are being examined at intervals, the third tube is not disturbed and serves as a check on the end point observed in the other tubes. Errors in technic tend to hasten coagulation. Normally by this method the coagulation time is 6 to 12 minutes.

Prolongation of coagulation time occurs notably in hemophilia, and to a less extent in melena neonatorum, obstructive jaundice and some anemias.

Prothrombin Time (Howell).—Blood is withdrawn in the manner described for the determination of coagulation time by Howell's method. Four c.c. of blood are emptied into a centrifuge tube containing 0.5 c.c. of a 1 per cent oxalate solution (made up in 0.9 per cent sodium chloride). After mixing the specimen, the tube is centrifugalized for a length of time sufficient to secure a clear plasma. This plasma is pipeted off and 5 drops are placed in each of 4 tubes. To these are added 0.5 per cent calcium chloride solution, 2, 3, 4 and 5 drops respectively. They are then gently mixed.

The prothrombin time is the earliest moment at which one of the tubes can be inverted without spilling its contents. The test should be controlled by carrying out similar observations on normal blood. The minimum time in normal blood is 9 to 12 minutes. With hemophilic blood the time required for coagulation to occur is greatly prolonged, being as long as 2 to 5 hours.

Calcium Time (Lee and Vincent).—This test is useful in determining

whether calcium therapy can be expected to be any value in cases in which there is a delayed coagulation time.

A few cubic centimeters of blood are obtained in the manner described and 1 c.c. is placed in each of two Wassermann tubes (8 to 10 mm. in diameter). To one of these, 3 drops of 1 per cent calcium chloride solution are added and the coagulation time in the two tubes noted. Should the time required for coagulation be less in the tube to which calcium has been added, the prolongation of coagulation time may be assumed to be due, in part at least, to a deficiency in calcium.

THE ESTIMATION OF INCREASED BLOOD DESTRUCTION

The Study of the Pigment Metabolism.—Evidence of increased blood destruction may be gained by the examination of blood for bilirubin as by the van den Bergh and icterus index tests, and the examination of the urine and stools for urobilin. A great deal of emphasis has in the past been laid on the value of these methods for the study of diseases of the liver and bile passages, but it should be borne in mind that they are equally important in the functional study of the hematopoietolytic system. An excess of bile pigment in the blood stream indicates obstruction to the normal excretion of bile, damage to the liver cells or excessive blood destruction. The icterus index test measures quantitatively the degree of bilirubinemia and, when the other causes mentioned have been ruled out, indicates the amount of blood destruction. The van den Bergh test serves the same purpose and furthermore facilitates the differentiation of the obstructive and nonobstructive types of bilirubinemia. It is superior to the icterus index test inasmuch as it is not quantitatively altered by hemolysis, lipemia or other pigments such as carotin. Excessive quantities of urobilin in the feces and urine likewise point to excessive blood destruction. The importance of such tests in the differentiation of hemolytic from nonhemolytic types of anemia will be discussed in subsequent chapters. As all of these tests have already been described in Volume II, they will not be further considered here.

Determination of the Fragility of Erythrocytes (Giffin and Sanford).—The determination of the resistance of red corpuscles to hemolysis is carried out by subjecting them to varying strengths of sodium chloride solution and determining the point at which hemolysis begins and that at which it is complete. For this test a 0.5 per cent solution of chemically pure sodium chloride is required.* Twelve tubes numbered from left to right, 25, 24, 23 . . . 14, are set up in each of two racks. With a capillary pipet a number of drops of 0.5 per cent sodium chloride solution corresponding to the number on the tube is placed in each. Distilled water is then added with the same pipet so that the total number of drops in each tube is 25. The strength of the solution of sodium chloride in each tube is, then, equal to the number of the tube multiplied by 0.02.

Blood is withdrawn from a vein of the patient with a dry, sterile syringe and one drop is placed in each tube. Blood should be obtained from a normal individual as well and a control test carried out in the second rack of tubes.

After the racks have been allowed to stand for two hours at room temperature, they may be read. Beginning hemolysis is indicated by a slight reddish coloring which has resulted from the laking of the least resistance cells. Complete hemolysis is indicated by a clear red solution and the absence of any corpuscular residue on shaking the tube.

Normal blood shows commencing hemolysis at 0.44 per cent to 0.38 per cent sodium chloride solution and complete hemolysis at 0.36 per cent to 0.32 per cent. Increased fragility is found notably in hemolytic jaundice.

MISCELLANEOUS EXAMINATIONS

The Specific Gravity and the Viscosity of Blood.—The specific gravity of the blood in healthy adults varies between 1.050 and 1.060 and is slightly higher in men than in women, the average for the former being 1.057, while for the latter it is 1.055. Barbour and Hamilton have recently described a very simple method for determining specific gravity. Although distinct variations are noted

* This solution should be made from sodium chloride which has been weighed after it has been dried.

in disease it has not as yet been shown that the determination of blood specific gravity yields any information of clinical importance which cannot be gained by other more commonly used examinations.

The normal viscosity of blood is, as compared with that of distilled water, about 4.5. Like specific gravity it is reduced in the anemias, nephritis and cachectic conditions generally. It is increased in acute febrile diseases, diabetes mellitus, obstructive jaundice and in any condition associated with polycythemia.

The Sedimentation Rate of Corpuscles.—That variations take place in the rate at which the red corpuscles in noncoagulable blood "sediment" or settle out from the plasma has long been known, but it was not until Fahraeus in 1918 attempted to make use of this phenomenon for the early diagnosis of pregnancy that general interest in the test was aroused. Since that time the relation of the blood sedimentation rate to many diseases has been studied and several important observations have been made.

In health the rate of sedimentation is very slow. As compared with the blood of a healthy young adult, it is somewhat more rapid in the newly-born and in old age. During the menstrual period there is some acceleration and a distinct increase in rate occurs from the third or fourth month of pregnancy onward. In disease a reduction in the suspension stability of the blood is one of the most common general reactions of the organism. Fahraeus says, "In this respect it may best be compared with such reactions as pyrexia and leukocytosis. The increased sinking velocity has many features in common with these phenomena without running parallel to either of them. It occupies, therefore, an entirely independent position in clinical symptomatology. On account of its completely nonspecific character, the reaction has, as a rule, proved less instructive in respect to the diagnosis of the disease than as regards the activity or intensity of the morbid process."

The exact nature of the phenomenon of sedimentation is little understood. The reaction is nonspecific and is a complex biologic process which depends on a variety of factors. In an excellent monograph in which he reviews his own as well as the experiments of others, Fahraeus points out that the factor which is most important in influencing the suspension stability of blood is the radius of the suspended particles. He furthermore shows that the aggregation of red corpuscles or rouleaux formation is greater in disease than in health and that not only is the tendency to rouleaux formation greater but the rouleaux are larger and more tightly packed. Fahraeus found a complete parallelism between the suspension stability of blood and the tendency to rouleaux formation. The latter tendency appears to be directly related to the fibrinogen content of the blood.

Rourke and Plass have recently shown that the inorganic anticoagulants decrease the rate of settling in proportion to their concentration; that centrifugalizing blood for 20 minutes at 2500 revolutions per minute does not affect its settling velocity after remixing; that the dilution of blood (with its own plasma) leads to more rapid settling of the cells; that increase of temperature (within certain limits) makes for more rapid sedimentation but that within the range of ordinary room temperatures the changes are hardly significant. On the other hand, changes in the rate of settling due to the ingestion of food are slight, and short, violent exercise has an insignificant and variable effect. Greisheimer and her coworkers have found that as the red cells decrease in number the sedimentation rate increases, but do not consider this factor causal.

It is obvious that a nonspecific phenomenon which is so little understood must be interpreted with caution. Nevertheless, certain statements seem to be well substantiated empirically. Thus Cutler has found the test of distinct value in estimating activity in tuberculous infection and, through frequent repetition, it appears to be of great value in determining progress. Cutler found the sedimentation test to be of greater value in these respects than the observation of temperature, pulse or weight. Wingfield and Goodman point out that the test has its greatest value in tuberculosis in the examination of patients who cannot be closely observed clinically. Again, in gynecologic conditions Baer and Reis found the test more useful than the temperature curve or the leukocytes in determining the presence or absence of infection. Among others, Polak and Maz-

zola have shown that the sedimentation rate is useful as a prognostic index and is a valuable aid in determining a safe time for operation. Schilling points out that the sedimentation test is of little value in the study of acute infections since it reacts much more slowly than the leukocytic picture, but, on the other hand, it is of great value in the detection of chronic infection for in the presence of the latter the leukocytic picture may be normal whereas the sedimentation rate is almost always accelerated. Gram feels that the test is most important in calling attention to more or less occult diseases of infectious or toxic origin. Again, the test appears to be of some value in distinguishing organic disease and functional disorders. Normal sedimentation rate is found in functional as compared with organic diseases, in hysteria, neurasthenia and various psychoses.

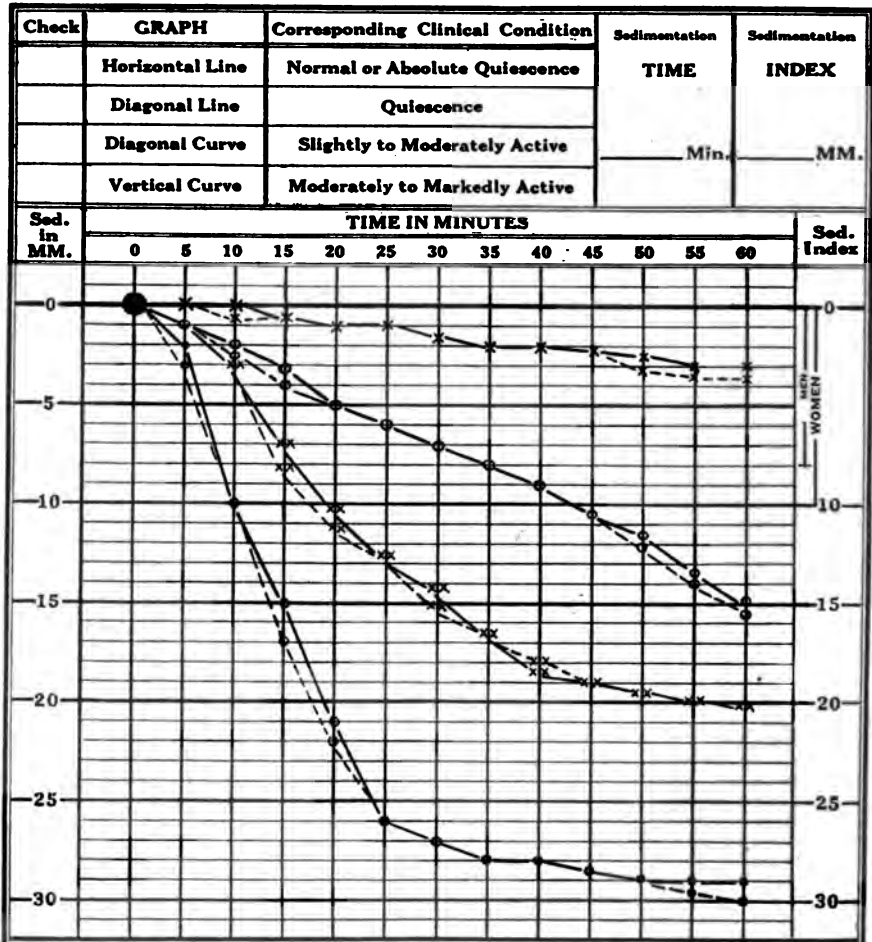


FIG. 28.—SEDIMENTATION CHART. (Cutler, *Am. Rev. Tuberculosis*.)

Sedimentation rate is delayed in conditions associated with marked increases in the number of red and white corpuscles.

A great number of methods have been described for carrying out the sedimentation test and a great variety of instruments may be purchased. Generally speaking, the methods used have depended on either the observation of the rate (Linzenmeier method) or the degree to which sedimentation occurs (Westergren method).

Since Cutler has shown that alterations take place in sedimentation velocity from minute to minute, it is preferable to observe both the rate and the degree of sedimentation. Blood is obtained from the vein of a patient as already described. The nature of the anticoagulant is unimportant as long as the same quantity is used each time. The blood is placed in one of the special sedimentation tubes or in a graduated tube such as a graduated centrifuge tube, a graduated 1 c.c. pipet* or the Wintrobe hematocrit. It is necessary of course to fill the tube to exactly the same point each time it is used as otherwise results cannot be compared. The tube is allowed to stand vertically and the height of the column of red corpuscles is read at 5 or 10 minute intervals for one hour. The readings are plotted on a graph. In health a practically horizontal line is obtained. Thus, if a 1 c.c. graduated pipet is filled with a column of blood 15 mm. high, it will be found that in a normal individual there will be no more than 2 to 8 mm. sedimentation at the end of an hour. In the presence of infection, depending to a great extent on the severity, sedimentation will commence sooner and will be more marked so that a "diagonal line," a "diagonal curve" or a "vertical curve" will result (Cutler) (Fig. 28).

Gram, and Rourke and Ernstene have recently published charts by means of which the sedimentation rate can be corrected for variations associated with differences in hemoglobin percentage and in cell volume percentage, respectively. Gram feels that such corrections are important as otherwise an increased sedimentation rate may be masked by a high red cell count or, *vice versa*, the sedimentation time may appear to be greatly increased when the accelerated sinking velocity is largely due to the anemia present.

BIBLIOGRAPHY

- BAER, J. L. AND REIS, R. A.: Further studies in sedimentation, *Am. J. Obst. & Gynec.*, 12: 740-744, 1926.
 BANTAI, A. L. AND ANDERSON, S. V.: Erythrocyte sedimentation test in tuberculosis, *Arch. Int. Med.*, 46: 787-796, 1930.
 BARBOUR, H. G. AND HAMILTON, W. F.: The falling drop method for determining specific gravity of fluids, *J. Biol. Chem.*, 69: 625-640, 1926.
 BEACOM, D. N.: A modification of Goodpasture's technic for the peroxidase reaction in blood smears, *J. Lab. & Clin. Med.*, 11: 1092-1093, 1926.
 BERMAN, L.: The determination of hemoglobin by the acid hematin method, *Arch. Int. Med.*, 24: 553, 1919.
 CAPPS, J. A.: A study of volume index. Observations upon the volume of erythrocytes in various disease conditions, *J. M. Research*, 5: 367-401, 1903.
 COHEN, B. AND SMITH, A. H.: The colorimetric determination of hemoglobin, *J. Biol. Chem.*, 39: 489, 1919.
 CUNNINGHAM, R. S., SABIN, FLORENCE R., SAGIYAMA, S. AND KINDWALL, J. A.: The role of the monocyte in tuberculosis, *Bull. Johns Hopkins Hosp.*, 37: 231-280, 1925.
 CUTLER, J.: Graphic presentation of blood sedimentation test; study in pulmonary tuberculosis, *Am. J. M. Sc.*, 171: 882-901, 1926.
 —: The graphic method for the blood-sedimentation test, *Am. Rev. Tuberc.*, 19: 544-558, 1929.
 DUKE, W. W.: The pathogenesis of purpura hemorrhagica with especial reference to the part played by blood-platelets, *Arch. Int. Med.*, 10: 445-469, 1912.
 DUPRAY, M.: A colorimetric method for the determination of iron and hemoglobin in the blood, *J. Lab. & Clin. Med.*, 12: 917-920, 1927.
 EMMONS, W. F.: Clinical perimometer, *Quart. J. Med.*, 21: 83, 1927.
 ERNSTENE, C.: Erythrocyte sedimentation, plasma fibrinogen and leukocytosis as indices of rheumatic infection, *Am. J. M. Sc.*, 180: 12, 1930.
 EVE, F. C.: Early diagnosis of pernicious anemia by halometer, *Brit. M. J.*, 2: 48, 1929.
 FAHRBAUS, R.: Ueber die Ursachen der verminderten Suspensionsstabilität der Blutkörperchen während der Schwangerschaft, *Biochemische Zeitschrift*, 89: 355-364, 1918.
 —: The suspension stability of the blood, *Physiol. Rev.*, 9: 241-274, 1929.
 FOWWEATHER, F. S.: The determination of iron in blood, tissues and urine, *Biochem. J.*, 20: 93-98, 1926.
 FRIEDLANDER, A. AND WIEDEMER, CHARLOTTE: The reticulocyte count in normal and in abnormal conditions, *Arch. Int. Med.*, 44: 209-228, 1929.
 GIFFIN, H. Z. AND SANFORD, A. H.: Clinical observations concerning the fragility of erythrocytes, *J. Lab. & Clin. Med.*, 4: 465, 1919.
 GOODPASTURE, E. W.: A peroxidase reaction with sodium nitroprusside and benzidine in blood smears and tissues, *J. Lab. & Clin. Med.*, 4: 442, 1919.
 GRAHAM, G. S.: Benzidine as a peroxidase reagent for blood smears and tissues, *J. M. Research*, 39: 15, 1918.
 GRAM, H. C.: The sedimentation of the blood corpuscles in various internal diseases and the result of the correction of this value for the variations of the hemoglobin percentage, *Acta med. Scandinav.*, 70: 242, 1929.
 GRISHAMER, ESTHER M., RYAN, MARY AND JOHNSON, OLGA H.: The relationship between cell count and sedimentation index, *Am. J. Physiol.*, 89: 170-175, 1929.
 —, JOHNSON, OLGA AND RYAN, MARY: The relationship between sedimentation index and fibrin content in relatively normal individuals, *Am. J. M. Sc.*, 177: 816-827, 1929.
 * Leakage is conveniently prevented by placing a rubber band about the pipet.

- HADEN, R. L.: Accurate criteria for differentiating anemias, *Arch. Int. Med.*, 31: 766-780, 1923.
- : The technic of determination of the relative mass, the individual cell volume, and the volume index of the erythrocytes of man, *J. Lab. & Clin. Med.*, 15: 736-746, 1930.
- : The value of volume index in the diagnosis of pernicious anemia, *J. Am. M. Ass.*, 83: 671-674, 1924.
- HALDANE, J.: The colorimetric determination of hemoglobin, *J. Physiol.*, 26: 497, 504, 1900-1901.
- HALL, BYRON E.: A critical review of the hematological literature dealing with the results of the supravital staining method, *Folia. Haemat.*, 43: 206-234, 1930.
- HELLIG, E.: Hemometer, *München. med. Wchnschr.*, 71: 1821, 1924.
- HOWELL, W. H.: Condition of the blood in hemophilia, thrombosis and purpura, *Arch. Int. Med.*, 13: 76-95, 1914.
- JACKSON, E. D.: Blood sedimentation test in gynecology, *J. Obst. & Gynec. Brit. Emp.*, 37: 547, 1930.
- JACOBSON, V. C.: A new standard solution for Sahli's modification of Gower's hemoglobinometer, *J. Am. M. Ass.*, 73: 1282, 1919.
- LEE, R. I. AND VINCENT, BETH: The relation of calcium to the delayed coagulation of blood in obstructive jaundice, *Arch. Int. Med.*, 16: 59-66, 1915.
- AND WHITE, P. D.: A clinical study of the coagulation time of the blood, *Am. J. M. Sc.*, 165: 495-503, 1913.
- LINZENMEIER, G.: Rapidity of sedimentation of red blood corpuscles and its practical value, *München. med. Wchnschr.*, 70: 1243-1245, 1923.
- MILLAR, W. G.: The differentiation method of measuring the diameters of erythrocytes, *Proc. Roy. Soc.*, 99: 264, 1925.
- NEWCOMER, H. S.: Absorption spectra of acid hematin, oxyhemoglobin and carbon monoxide hemoglobin. A new hemoglobinometer, *J. Biol. Chem.*, 37: 465, 1919.
- : A new optical instrument for the determination of hemoglobin, *J. Biol. Chem.*, 55: 569-574, 1923.
- OLEF, ISADORE: Blood platelets, *Arch. Int. Med.*, 46: 585-596, 1930.
- OSGOOD, E. E. AND HASKINS, H. D.: A new permanent standard for estimation of hemoglobin by the acid hematin method, *J. Biol. Chem.*, 57: 107-110, 1923.
- PALMER, W. W.: The determination of hemoglobin, *Proc. Soc. Exper. Biol. & Med.*, 14: 175, 1917.
- PIJPER, ADRIANUS: An improved diffraction method for diagnosing and following the course of pernicious and other anemias, *Brit. M. J.*, 1: 635, 1929.
- POLAK, J. O. AND MAZZOLA, V. P.: Clinical significance of sedimentation tests as diagnostic and prognostic sign, *Am. J. Obst. & Gynec.*, 12: 700-705, 1926.
- PONDER, ERIC AND MILLAR, W. G.: The measurement of the diameters of erythrocytes. I. The mean diameter of the red cells in man, *Quart. J. Exper. Physiol.*, 14: 67, 1924.
- PRICE-JONES, C.: The diurnal variation in the sizes of red blood cells, *J. Path. & Bact.*, 23: 371, 1920.
- REES, H. M. AND ECKER, E. E.: An improved method for counting blood platelets, *J. Am. M. Ass.*, 80: 621-622, 1923.
- ROBSCHEIT, F. S.: A comparative study of hemoglobin determination by various methods, *J. Biol. Chem.*, 41: 209, 1920.
- ROURKE, M. DOROTHY AND ERNSTENE, A. C.: A method for correcting the erythrocyte sedimentation for variations in the cell volume percentage of blood, *J. Clin. Investigation*, 8: 545, 1930.
- AND PLASS, E. D.: An investigation of various factors which affect the sedimentation rate of the red blood cells, *J. Clin. Investigation*, 7: 365-368, 1929.
- SABIN, FLORENCE R.: Studies of living human blood-cells, *Bull. Johns Hopkins Hosp.*, 34: 277-288, 1923.
- , AUSTRIAN, C. R., CUNNINGHAM, R. S. AND DOAN, C. A.: Studies on the maturation of myeloblasts into myelocytes, *J. Exper. Med.*, 40: 845-871, 1924.
- , CUNNINGHAM, R. S., DOAN, C. A. AND KINDWALL, J. A.: The normal rhythm of the white blood-cells, *Bull. Johns Hopkins Hosp.*, 37: 14-67, 1925.
- SATO, A. AND SEKIYA, S.: A simple method for differentiation of myeloid and lymphatic leukocytes of human blood, *Tohoku J. Exper. Med.*, 7: 111, 1926.
- SCHILLING, VICTOR: *The Blood Picture and Its Clinical Significance*. Translated by R. B. H. Gradwohl, Ed. 78, St. Louis, C. V. Mosby Company, p. 68, 1929.
- SCHWENTKER, FRANCIS F.: The estimation of hemoglobin. A new hemoglobinometer, *J. Lab. & Clin. Med.*, 15: 247-259, 1929.
- SHEARD, CHARLES AND SANFORD, A. H.: Photo-electrometer with one stage of amplification, as applied to the determination of hemoglobin, *J. Am. M. Ass.*, 93: 1951-1957, 1929.
- TERRILL, E. H.: On the colorimetric determination of hemoglobin with especial reference to the production of a standard, *J. Biol. Chem.*, 53: 179-191, 1922.
- VAN ALLEN, C. M.: An hematocrit method, *J. Lab. & Clin. Med.*, 10: 1027-1040, 1925.
- : The volume measurement of blood platelets, *J. Lab. & Clin. Med.*, 12: 282-285, 1926.
- VAN SLYKE, D. D.: A method for the determination of carbon dioxide and carbonates in solution, *J. Biol. Chem.*, 80: 347-368, 1917.
- : Gasometric determinations of the oxygen and hemoglobin of blood, *J. Biol. Chem.*, 33: 127, 1918.
- AND STADIE, W. C.: The determination of gases of the blood, *J. Biol. Chem.*, 49: 1-42, 1921.
- WESTERGREN, A.: The technique of the red cell sedimentation reaction, *Am. Rev. Tuberc.*, 14: 94-101, 1926.
- WILLIAMSON, C. S.: Influence of age and sex on hemoglobin, *Arch. Int. Med.*, 18: 505, 1916.
- WINGFIELD, R. C. AND GOODMAN, R.: Rate of sedimentation of red blood corpuscles in pulmonary tuberculosis, *Lancet*, 2: 805-806, 1926.
- WINTROBE, M. M.: A simple and accurate hematocrit, *J. Lab. & Clin. Med.*, 15: 287-289, 1929.
- : The direct calculation of the volume and hemoglobin content of the erythrocyte. A comparison with color index, volume index and saturation index determinations, *Am. J. Clin. Path.*, 1: 147-165, 1931.
- : The erythrocyte in man, *Medicine*, 9: 195-255, 1930.
- : The volume and hemoglobin content of the red blood corpuscle, *Am. J. M. Sc.*, 177: 513-523, 1929.
- WONG, SAN YIN: Colorimetric determination of iron and hemoglobin in blood, *J. Biol. Chem.*, 77: 409-412, 1928.

CHAPTER III

DISEASES ASSOCIATED CHIEFLY WITH ALTERATIONS IN THE RED CORPUSCLES

By JOHN H. MUSSER, M.D., AND MAXWELL M. WINTROBE, M.D.

- THE ANEMIAS**, p. 799—Definition, p. 799—Classification, p. 800—General symptomatology, p. 801—Pallor, p. 801—Respiratory and circulatory systems, p. 802—Nervous system, p. 803—Gastro-intestinal system, p. 804—Urogenital system, p. 804—Metabolism, p. 804.
- Acute posthemorrhagic anemia**, p. 804—Definition, p. 804—Etiology, p. 804—Symptomatology, p. 804—Diagnosis, p. 805—Prognosis, p. 805—Treatment, p. 806.
- Chronic posthemorrhagic anemia**, p. 806—Definition, p. 806—Etiology, p. 806—Symptomatology, p. 807—Blood changes, p. 807—Diagnosis, p. 807—Treatment, p. 808.
- The treatment of anemia**, p. 808—General measures, p. 808—Diet in anemia, p. 809—Iron and accessory factors, p. 813—Arsenic, p. 815—Blood transfusion in anemia, p. 815.
- Simple chronic anemia**, p. 818—Definition, p. 818—Etiology, p. 818—Symptomatology, p. 819—Blood changes, p. 819—Diagnosis, p. 819—Treatment, p. 819—Prognosis, p. 820—Simple achlorhydric anemia, p. 820.
- Chlorosis**, p. 820—Definition, p. 820—Etiology, p. 820—Symptomatology, p. 821—Blood changes, p. 822—Diagnosis, p. 822—Complications and sequelae, p. 823—Treatment, p. 823—Prognosis, p. 823—Pathology, p. 823.
- Aplastic anemia**, p. 823—Synonyms, p. 823—Definition, p. 823—Etiology, p. 823—Idiopathic aplastic anemia, p. 824—Symptomatology, p. 825—Blood changes, p. 825—Diagnosis, p. 825—Treatment, p. 826—Prognosis, p. 826—Pathology, p. 826.
- Myelophthisic anemia**, p. 826.
- Pernicious anemia**, p. 827—Synonyms, p. 827—Definition, p. 827—Etiology, p. 827—Symptomatology, p. 830—Laboratory findings, p. 832—Diagnosis, p. 836—Complications, p. 837—Treatment, p. 837—Prognosis, p. 840—Pathology, p. 840—History, p. 841.
- Hemolytic anemias**, p. 841—Definition, p. 841—Pathologic physiology, p. 841—Symptomatology, p. 842—Acute hemolytic anemia, p. 842—Chronic hemolytic anemia, p. 843.
- Sickle cell anemia**, p. 844—Definition, p. 844—Etiology, p. 844—Symptomatology, p. 845—Laboratory findings, p. 846—Diagnosis, p. 846—Treatment, p. 847—Prognosis, p. 847—Pathology, p. 847.
- The anemias of childhood**, p. 847.
- POLYCYTHEMIA**, p. 849—Definition, p. 849—Relative polycythemia, p. 849—Absolute polycythemia, p. 849.
- Erythrocytosis**, p. 849.
- Erythremia**, p. 850—Synonyms, p. 850—Definition, p. 850—Etiology, p. 850—Symptomatology, p. 850—Laboratory findings, p. 851—Diagnosis, p. 852—Treatment, p. 852—Prognosis, p. 853—Pathology, p. 853—History, p. 853.

THE ANEMIAS

Definition.—Although the term anemia, strictly speaking, means a lack of blood and thus might be applied to any condition in which there is a reduction below the normal in the total quantity of blood, it has come to be applied more specifically to those conditions in which there is a deficiency in the number of red corpuscles, the amount of hemoglobin or the relative volume of packed red cells per unit of volume.

When the anemia is not marked there may be a reduction in the quantity of hemoglobin and the volume of packed red cells without any reduction in the num-

ber of red corpuscles; or the reverse of this may be found. When the anemia is marked all three factors are affected, but the relative reductions differ in the various types of anemia. Thus in pernicious anemia the reduction in the number of red cells is more marked, relatively, than the reduction in quantity of hemoglobin or volume of packed red cells. This denotes that the red corpuscles, while reduced in number, are on the whole larger and contain more hemoglobin as compared with normal red cells. On the other hand, in the anemia associated with chronic blood loss the reduction in number of cells is slight when compared to the reduction in the volume of packed red cells, and particularly in comparison to the diminution in hemoglobin. In this type of anemia the corpuscles are generally small and contain inadequate quantities of hemoglobin. Between these two extremes several grades of changes are found in other types of anemia.

To the condition in which the blood as a whole is reduced in amount, the term *oligemia* has been applied. *Oligocythemia* refers to a deficiency in the number of red corpuscles, while *oligochromemia* signifies a reduction in the quantity of hemoglobin. These terms are now little used.

Classification.—Anemia is not a disease in itself but simply a state of the blood which results from the activity of a larger number of noxious agents. Frequently the state of the circulating blood is the result of some form of injury to the erythropoietic tissue of the bone marrow; less often is it due to actual destruction or loss of blood. Anemia being a symptom of diseases produced by a great variety of etiologic agents the nature of many of which is little understood, there is little wonder that the classification is at present unsatisfactory. The time-worn division of anemia into primary and secondary types is totally inadequate. By *primary anemia* was meant an anemia originating in and primarily involving the blood and the blood-making organs. The term has also been employed to denote an anemia of which the cause is unknown as distinguished from *secondary anemia* which is the type resulting from some known cause or one which does not primarily affect the blood. Since this classification covers up our ignorance concerning the "primary" anemias, makes no attempt to subdivide the various types of "secondary" anemia and has no intrinsic merit whatever, it should no longer be employed.

A more logical classification is the following:

(a) Anemia associated with acute, chronic or chronically intermittent *blood loss* whether this is in the form of external hemorrhage or hemorrhage into the lumen of the gastro-intestinal tract, the respiratory or the genito-urinary passages.

(b) Anemia resulting from *defective blood formation*. The anemia associated with many systemic diseases is frequently of this type. The defective formation may be the result of injury to the bone marrow or is the result of an inadequate supply of building materials. The response of certain types of anemia to adequate quantities of iron or liver suggests that they are of this type. In some of the diseases which fall into this group anemia is present in spite of great activity on the part of the bone marrow, whereas in other forms the bone marrow appears to be totally aplastic (aregenerative).

(c) Anemias resulting from the destruction of blood within the body, the so-called *hemolytic anemias*. In this group might be included the acute hemolytic anemias resulting from sepsis, parasitic invasion and various poisons; the chronic anemia associated with the disease known as hemolytic jaundice; and, most important of all, pernicious anemia.

The inclusion of pernicious anemia in the last-named class illustrates a fundamental defect in this classification. Although during the periods of relapse of this disease greatly increased blood destruction occurs, the response to the administration of adequate quantities of liver suggests that in pernicious anemia there is defective blood formation and that hemolysis is a secondary phenomenon. Likewise it is sometimes difficult to classify other anemias since blood loss, defective blood formation and excessive blood destruction may all be associated in a single instance.

Since the diagnosis of anemia is very generally made from the examination of the blood itself, a very useful classification would be one that is based on

morphologic differences. Recent work, particularly that of Price-Jones, has emphasized a fundamental morphologic difference between pernicious anemia and other forms of anemia. In this disease the red cells are characteristically large and so the term "macrocytic" has been suggested to distinguish this from other types of anemia. Recent observations of the differences in the size and hemoglobin content of the red corpuscles in anemia suggest that the following classification may be followed (Wintrobe): (1) *Macrocytic* anemia, in which the corpuscles are, on the average, abnormally large and well filled with hemoglobin; this group includes pernicious anemia, sprue, the "pernicious anemia" of pregnancy and several rarer forms of anemia. (2) *Normocytic* anemias in which, although the total number of cells is reduced, there is no marked alteration in their average size or hemoglobin content; this class includes anemia resulting from acute blood loss, aplastic and semi-aplastic anemias. (3) *Simple microcytic* anemias in which the corpuscles are smaller than normal and contain less hemoglobin than is normal. This type of anemia is distinguished from the fourth group by the fact that the reduction in the hemoglobin content is no greater than the reduction in size. The simple chronic anemia associated with various chronic infections and intoxications falls into this group. (4) *Hypochromic microcytic* anemias in which the reduction in hemoglobin content is even more marked than the reduction in size with the result that the corpuscular hemoglobin concentration is reduced. In this last group the anemia associated with chronic blood loss is found.

Another, more complex, morphologic classification of anemia has been suggested by Berglund and Watkins. The reader is referred to the papers of these investigators as well as to those of Wintrobe for a more complete description of these classifications.

It is not unlikely that morphologic distinctions will be of value not only for diagnosis but also as a guide to treatment, since it appears that there are marked differences in the response of macrocytic as compared with other types of anemia to the different therapeutic measures now employed. However, it must be borne in mind that there is a large element of transition in the clinical picture attending the development and course of the anemias. Wide variations occur and unless a classification is evolved which recognizes these variations and does not overemphasize the diagnostic significance of certain individual morphologic departures from the normal in the cellular elements of the blood, a useful subdivision cannot be hoped for.

General Symptomatology.—For the greater part the production of symptoms in all cases of anemia is dependent fundamentally and chiefly upon the loss of the oxygen-carrying and -combining power of the blood and the consequent interference with cell nutrition and function.* The degree of impairment of function varies not only with the severity of the anemia but also with the nature of the ailment. The red cell count itself is not an index of the symptoms that may be expected. Patients suffering from pernicious anemia may be up and about when their cell count is surprisingly low, whereas other individuals may have many complaints when the number of cells is only slightly reduced.

PALLOR.—In general the most striking outward symptom of anemia is pallor. This is manifest frequently in the skin but more constantly in the buccal and pharyngeal mucous membranes, the conjunctivae and the lips. The bed of the finger nail, the palms of the hands and the lobes of the ears are also points at which pallor is very noticeable in anemia. In the case of profound acute blood loss this is seen as a waxy dead whiteness of the skin and pale mucous membranes. In chronic intermittent blood loss there is a distinctly sallow color. In Addisonian pernicious anemia the high grade of hemolysis present is responsible no doubt for the peculiar lemon-yellow pallidity so commonly observed in the more advanced or well established cases of this disease, a color so striking as almost to be pathognomonic when present in this typical form. In chlorosis the typical color, from which the disease derives its name, is a peculiar greenish

* In this and subsequent sections we have made free use of material from the section on Diseases of the Blood by the late Dr. Charles Lyman Greene which this replaces.

sallowness, but this color is often lacking and, furthermore, a not inconsiderable number of cases of chlorosis show red cheeks (*chlorosis rubra*). In leukemia pallor is usually marked and may be associated with a greyish tint of the skin.

The pallor associated with various systemic diseases is often quite characteristic. In Bright's disease with anemia the color variations associated with the different types and stages of the ailment are marked. In acute Bright's disease with general edema one meets with a curious pasty white skin even when little or no true anemia is present. In these cases the peculiar dead white skin of the legs may be traversed and overlaid by venules in such a manner as to justify the old-fashioned term "marble-like" as applied to the underlying edema present. Certain forms of Bright's disease of the chronic type result in a peculiar fawn-colored skin. The usual form of chronic nephritis without edema, even though it be associated with a considerable degree of anemia, may give little evidence of it outwardly, the appearance of the patient being oftentimes that of robust and even florid health.

In malignant disease the degree of anemia varies widely, but in some instances reaches a high grade and, especially in certain cases of carcinoma of the stomach with metastases in the liver, may be so extreme as to simulate closely pernicious anemia. In such cases, however, the outward appearance is usually that characteristic of malignancy, namely, a peculiar earthy, muddy pallor.

In general, the anemia of syphilis presents no striking characteristics, but in certain congenital and tertiary cases the anemia may be marked and carried over long periods of time with the result that there is produced in the skin, of the face especially, a peculiar sallow pallor difficult to describe yet quite characteristic and when once seen not likely to be forgotten.

In mitral regurgitation, and especially in mitral stenosis, an existing anemia may be masked by the misleading redness of the patient's cheeks and lips. This redness is not likely to deceive the experienced eye, however, inasmuch as it is darker than the flush of health and, in the lips, more intense. Frank advanced cases of aortic regurgitation may, by the curious pallor which most of them carry, bring about an erroneous assumption of existing anemia where none is present.

It should be borne in mind that skin pallor may be present without anemia. The color of the skin is determined by the degree and nature of its pigmentation, the thickness of the outer layers, the state of dilatation or contraction of the skin capillaries as well as by the amount and quality of the blood it contains. Mere pallor is extremely common in indoor workers even though the blood may be quite normal. Certain persons habitually have a pale skin. It was long assumed that the generally pallid appearance of persons residing in tropical and subtropical climates is the result of a climatic anemia. As has been mentioned in Chapter I, this section, recent accurate blood determinations have quite conclusively disproved this assumption and even suggest that the content of hemoglobin and red corpuscles in the blood in such a climate may be greater than in the more temperate zones. It is obvious, then, that persons may be pale, yet not anemic; ruddy, yet profoundly anemic; but never anemic with normal color in the visible mucous membranes.

RESPIRATORY AND CIRCULATORY SYSTEMS.—Respiratory symptoms in patients suffering from anemia may be very marked or, on the other hand, they may be noticeable only following exertion or excitement. The occurrence of respiratory symptoms depends on the rapidity of production of the anemia, on the severity of the anemia and, finally, on the associated myocardial changes. In cases of acute blood loss symptoms of oxygen deprivation develop when about 50 per cent of the blood has been lost. These symptoms depend largely on the decrease in the total blood volume and are to a large measure relieved when the loss of blood is replaced by absorption of fluid from the tissues or by the artificial introduction of fluid. When the anemia is of the chronic type, very marked reduction in hemoglobin may take place without the appearance of any respiratory symptoms except following exertion. In these cases more efficient utilization of the hemoglobin present in the blood as the result of increased

rate of blood flow and increased reduction of hemoglobin in the tissues are important compensatory factors.

In all severe types of anemia of long duration the myocardium must suffer to a greater or less degree, and one finds accordingly symptoms attributable to heart muscle insufficiency of varying degree in a large number of cases. Palpitation, breathlessness, tachycardia, or arrhythmia, syncopal attacks, precordial oppression and other subjective symptoms are often present and may constitute most troublesome complications. Only in the higher grades of anemia are we likely to find decided dyspnea which is attributable to the condition of the blood itself, and indeed in many instances it is difficult to determine to what extent an existing exertion dyspnea is to be credited to the accompanying myocardial weakness.

The heart itself is often dilated or markedly dilatable in cases of the profounder grades, and edema of the extremities is common in severe cases of chronic posthemorrhagic anemia or pernicious anemia. The pulse is usually of low tension, and in the more extreme cases of the severer types of anemia a systolic pressure of 80 mm. of mercury may be present.

In cases of marked posthemorrhagic anemia and in the pernicious type, one may encounter in its most typical form the curious humming "bruit de diable" over the vessels of the neck. In general, the murmurs associated with anemia are systolic in time, do not occupy all of systole and are maximal in the second pulmonary interspace, except in instances of extreme blood loss and acutely induced extreme blood deficit. Such murmurs are not widely transmitted and are well confined to the pulmonary field. Similar systolic murmurs may be audible over the aortic area and apex.

It is quite possible to understand that the greatly increased rapidity of the blood stream and the sharp reduction in specific gravity and viscosity encountered in anemias of the severe type may be adequate to explain the occurrence of these bruits. Nevertheless it is probable that other factors are contributory in most instances, the most important of these being the loss of tone in the myocardium and the increased rapidity of the heart beat. In the true murmurs of anemia any marked improvement in the condition of the blood is accompanied by a change for the better in any bruits present. It should be remembered in this connection that systolic murmurs may occur in the pulmonary area in the absence of anemia of a degree sufficient to be considered causative. Again, in many instances bruits, assumed primarily to be due to anemia, persist long after the blood has reached normal. This would indicate that impairment of myocardial tonus in itself may produce murmurs indistinguishable from those properly attributed to anemia.

NERVOUS SYSTEM.—A man or woman may suffer from the most extreme forms of anemia and die as the result of neurological changes without showing any decided nervous symptoms. On the other hand, cases showing relatively moderate degrees of anemia may present almost every symptom known in connection with a disturbed nervous system. Drowsiness, vertigo, extreme irritability, restlessness, perverted sensations, insomnia, mental depression, hysteria, neuralgia, headaches of all grades even to those so severe as to simulate meningitis, may sometimes be encountered in anemia of any type. Delirium is seldom seen except in terminal pernicious anemia or in the last stage of leukemia. There may be roaring in the ears and black spots before the eyes. Retinal hemorrhage occurs with some frequency in pernicious anemia, and in all severe forms of anemia the ophthalmoscope shows a pale fundus.

A great number of women, especially, go through life with a deficit of from 30 to 40 per cent of hemoglobin with or without a corresponding reduction in the erythrocytes, and in consequence fail at all times to enjoy health or to carry a normally functioning nervous system. This substandard physical state results in many instances in a chronic irritability of disposition and character which indirectly is a fertile source of mental ill health. It is responsible for the breeding of an innumerable number of neurotic or psychasthenic disorders.

GASTRO-INTESTINAL SYSTEM.—In anemia one encounters with considerable constancy symptoms referable to disturbed digestion, gastric or intestinal. In some instances these assume forms of great severity and are capable of seriously impairing nutrition. Anorexia, nausea, excessive appetite, flatulence, abdominal discomfort, constipation and diarrhea are the common manifestations.

Terminal Addisonian pernicious anemia is often associated with exhausting diarrheal attacks and intercurrent vomiting usually difficult to control and, of course, hastening a fatal issue. In the same cases paroxysmal abdominal pain occurs in about 50 per cent of the patients and constitutes oftentimes one of the most troublesome sources of complaint.

UROGENITAL SYSTEM.—Menstrual disturbances, most often amenorrhea, in the female and loss of libido in the male are frequently a manifestation of anemia. Albuminuria is not unusual and there may even be distinct renal functional impairment.

METABOLISM.—In chlorosis and in some forms of simple chronic anemia the superficial fat may be well preserved, giving the patient a misleading appearance of health in some instances, especially if he or she belongs to the ruddy group of anemics. In other types of anemia the state of nutrition is dependent upon the primary lesion. In pernicious anemia, even in its later stages, there exists oftentimes a wholly misleading appearance of fairly good nutrition due to the presence of subcutaneous fat; but the extreme pallor of the mucous membranes, the peculiar color of the skin, its velvety feel and, in most instances, the jelly-like consistency of the muscles should render any mistake impossible even in the absence of a blood count.

In severe anemias the basal metabolic rate may be increased. Such increases are especially marked in leukemia where the augmented metabolism depends probably on the excessive destruction of the white blood cells as well as on the increased consumption of oxygen by the overactive tissues and the excessive number of leukocytes.

ACUTE POSTHEMORRHAGIC ANEMIA

Definition.—This is an anemia due to the more or less sudden, rapid and extreme loss of blood or to rapidly repeated severe hemorrhage.

Etiology.—Sudden loss of blood and the consequent anemia may result from a large variety of causes such as those associated with trauma, the rupture of a peptic ulcer, typhoid fever and extra-uterine gestation. Again, the hemorrhage may be a symptom of one of the blood diseases such as hemophilia, purpura haemorrhagica or acute leukemia.

Symptomatology.—The clinical history will reveal the source of the hemorrhage or the picture of some illness will be presented in which blood loss may be suspected. The symptoms of anemia due to actual loss of blood must obviously vary widely with the amount of the hemorrhage and the condition of the individual at the time it occurs. Furthermore, the rate of flow must influence greatly the symptoms produced, introducing as it does the question of shock of greater or lesser severity. To a certain extent also the consciousness or unconsciousness of the patient at the time and his own temperament enter into the symptoms produced by any considerable hemorrhage. A concealed hemorrhage of which a nervous high-strung patient is wholly unaware may produce less shock than an open one in which the blood loss is much less. As a matter of practical importance one may add that in most instances the amount of blood lost in acute open hemorrhage is greatly overestimated by the patient and by those around him.

A robust adult has borne the loss of nearly or quite one-half his blood in certain instances, but the ability to withstand such drains is less at the younger ages and depends not only upon the previous state of health of the individual but also upon the rapidity of the flow, the degree of shock, the reduction of blood volume and other circumstances surrounding the hemorrhage. The loss of 1500 to 2000 c.c. of blood in a few hours may mean death, whereas as much as 60 per cent of the blood may be lost without death resulting if the hemorrhage is prolonged over 24 hours or more.

Aside from the psychic symptoms which result from loss of blood in a sensitive individual or the symptoms of the associated disease, acute blood loss is itself followed by extreme exhaustion and true shock with faintness or actual syncope, marked pallor, sighing, rapid shallow breathing, restlessness, and profuse sweating and thirst. The pulse becomes rapid and thready, the temperature subnormal and the blood pressure is markedly reduced.

The symptoms result chiefly from the reduction in the total blood volume and the suddenly induced oxygen shortage. The promptness with which the initial symptoms abate or subside following the cessation of bleeding, even though blood regeneration cannot have taken place, shows how great is this factor of diminished blood volume, how prompt is the adaptation of the tissues to the lesser volume under an emergency redistribution and how quickly blood volume is restored.

It must be remembered that even in considerable acute hemorrhages the factor of acute reduction in volume makes the blood count and hemoglobin estimation an uncertain guide, inasmuch as the amount of each in a given quantity of the blood may be affected but slightly. Immediately following the hemorrhage fluid passes from the tissues in an attempt to restore the normal volume of the blood. Furthermore, red corpuscles enter the blood stream from the various storehouses of the body, notably the spleen. These factors tend to confuse the blood picture, and decreasing values for the number of red corpuscles and quantity of hemoglobin may be found for several days following the hemorrhage in the face of other evidence of active blood formation. In such cases if total blood volume is measured and the total number of red corpuscles and the total quantity of hemoglobin calculated, it will be found that there is an actual increase in these values.

In addition to the changes mentioned, the immediate effect of a severe hemorrhage is marked stimulation of the bone marrow. Leukocytosis (14,000 to 20,000) of the neutrophilic type occurs within a few hours and may be present for 3 or 4 days or longer. Young forms of neutrophils appear and myelocytes and even myeloblasts may be found. The lymphocytes are unaffected. Likewise the blood platelets are increased and may amount to one million per cubic millimeter. Coagulation time is usually shortened.

Immediately following the hemorrhage no changes in the red corpuscles are observed. With improvement, evidence of erythropoiesis appears in the form of reticulocytosis (10 to 25 per cent), polychromatophilia, some variation in the size of the cells and even nucleated red corpuscles and some degree of poikilocytosis may be observed. The newly formed corpuscles are smaller than normal and contain less hemoglobin. As recovery takes place, the number of reticulocytes diminishes, the red cells more and more approach the normal, and the other signs of over-active blood formation gradually disappear. Frequently, however, following a very severe hemorrhage an entirely normal blood picture is not found again for several months. The percentage of reticulocytes is an important and delicate index of blood regeneration. Persisting high values suggest continued bleeding.

Diagnosis.—Usually the diagnosis of acute hemorrhagic anemia is readily made from the history and the whole symptom-complex. It is little aided by the examination of the blood itself except in that one of blood diseases, of which the hemorrhage may be a symptom, may be ruled out in this way.

Prognosis.—The outcome in a case of acute blood loss is dependent on a variety of factors. The age of the individual and the presence or absence of previous debilitating disease are important. A robust adult may be relieved of 1000 c.c. of blood without any untoward symptoms. Again, in the later period of pregnancy a much larger loss of blood may be withstood without untoward results than under normal circumstances. This may be related to the increased total volume of blood which Keith, Rowntree and Geraghty have found in the later months of pregnancy.

As has already been mentioned, the red cell count or hemoglobin estimation is of little value in gauging the severity of the hemorrhage. The character and

rapidity of the pulse are of much greater significance. In their studies of blood volume in wounded soldiers Robertson and Bock have shown that of all available tests, blood pressure readings are of most value as a guide to the severity of the hemorrhage. Their studies showed that when the volume of blood was reduced by the hemorrhage by less than 30 per cent, the effect of vasoconstriction was usually sufficient to maintain a normal blood pressure. When the blood volume was reduced below 70 per cent of normal, however, the blood pressure became subnormal and, in a general way, the reduction in blood pressure was proportional to the diminution in blood volume. From the study of a large number of wounded individuals the following rough equivalents were derived: (1) When the systolic blood pressure is 95 mm. the blood volume is less than 70 per cent of normal; (2) when the systolic blood pressure is 80 mm. the blood volume is usually 60 per cent of normal; (3) when the systolic blood pressure is below 80 mm. the blood volume is 54 to 60 per cent of normal. They found reduction of systolic blood pressure to 70 mm. to be a very grave prognostic omen.

Treatment.—The immediate indications in the treatment of acute blood loss are to **stop the bleeding, restore the blood volume and treat the shock.** Absolute rest in bed, **morphia** (unless specially contraindicated) and **warmth** are essential. Fluids should be administered by all the channels available, namely, by mouth, rectum, subcutaneously and intravenously. Robertson and Bock pointed out that unless the hemorrhage has been very excessive and the total hemoglobin of the body is reduced below 25 per cent, the **restoration of the blood volume is more important than the restoration of oxygen-carrying material.** From the total blood volume, gauged from the blood pressure in the manner already indicated, and the percentage of hemoglobin, the total quantity of hemoglobin in the blood may be roughly estimated. Thus when the systolic blood pressure is 95 mm., the total blood volume is approximately 70 per cent of normal. If the hemoglobin percentage is 50 per cent, then the total quantity of hemoglobin in this case is 35 per cent of normal. In such a case restoration of blood volume is the most important indication. When, however, the total hemoglobin percentage is reduced below 25 per cent, restoration of oxygen-carrying power is very essential, and **large transfusions, 500 c.c. or more, are advocated by these workers.**

During the Great War, **gum acacia solution (6 per cent) and even normal saline solution** were used for the restoration of blood volume. The use of gum solution, however, is not very satisfactory and may be followed by disagreeable reactions. The effect of hypodermoclysis is very evanescent. Wherever possible, therefore, even when the restoration of oxygen-carrying power is not primarily important, **blood transfusions** should be employed in the treatment of acute posthemorrhagic anemia, for in spite of many attempts to find a suitable substitute, this method of restoration of blood volume remains by far the best.

It is well to remember in the treatment of acute posthemorrhagic anemia that if the patient's condition is not critical and the bleeding has not been stopped, artificial restoration of blood volume may well be avoided since the low blood pressure will favor the spontaneous arrest of bleeding.

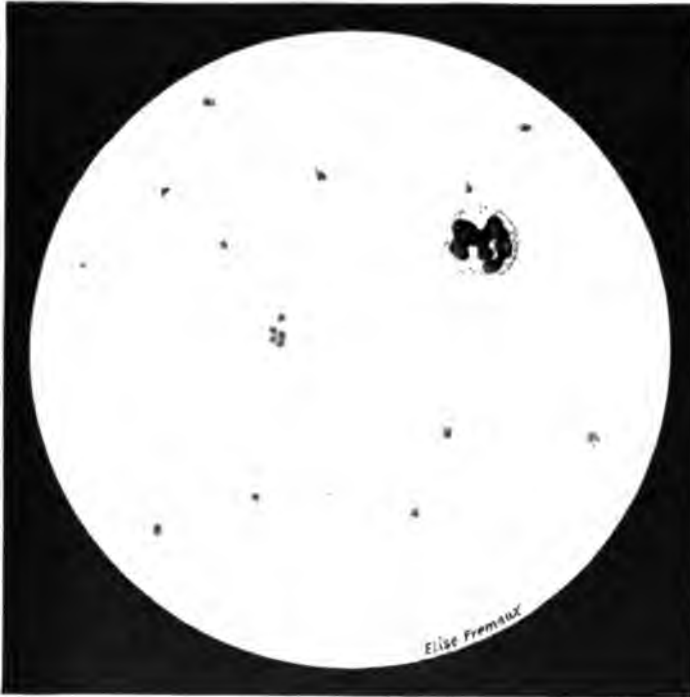
During the stage of recovery the treatment of acute posthemorrhagic anemia is the same as for that resulting from chronic blood loss.

CHRONIC POSTHEMORRHAGIC ANEMIA

Definition.—Anemia due to open or concealed hemorrhages of greater or less amount which occur so frequently as to prevent complete blood regeneration or exhaust the reparative powers of the blood-forming tissues is considered under this heading.

Etiology.—Among the many causes of this form of anemia are (a) bleeding hemorrhoids; (b) hemorrhage from the uterus such as results from the presence of uterine fibroids, carcinoma, polypi and the various other causes of excessive menstrual flow; (c) peptic ulcer, carcinoma of the bowel, hepatic cirrhosis; (d) recurrent severe epistaxis or repeated hemoptysis; (e) purpura, hemophilia and other blood diseases; (f) helminthiasis. The cause of the anemia

C. P. IV—Musser & Wintrobe.



CHRONIC POSTHEMORRHAGIC ANEMIA (WRIGHT'S STAIN). $\times 950$. COMPARE THE RED CORPUSCLES WITH THOSE SHOWN IN PLATE VI, FIG. A.

which is associated with hookworm infestation is still a matter of dispute, some investigators claiming that it is produced by a toxin elaborated by the parasite whereas others insist that it is due to long continued blood loss from the ulcerated mucous membrane of the bowel. Analogy suggests that this anemia is due to the latter cause since the blood picture resembles that observed in posthemorrhagic anemia (Wintrobe).

Symptomatology.—The general symptoms are those which have already been described as being common to all forms of anemia. The symptoms vary in degree with the severity of the anemia and the general condition of the patient. The result of chronic blood loss will vary with the amount of blood lost and, what is more important, with the interval of time which elapses between the periods of bleeding. If the intervals are of long enough duration complete regeneration of blood may take place and no symptoms will be produced. The daily loss of relatively small amounts of blood with the resulting continuous drain on the body is much more harmful than several relatively larger hemorrhages at intervals of weeks or months.

BLOOD CHANGES.—The blood findings necessarily vary with the severity of the anemia and the presence or absence of some associated debilitating disease such as carcinoma. The first effect of blood loss in small or moderate quantities is stimulation of the bone marrow. Immediately following the hemorrhage blood corpuscles may be liberated from the storehouses of the body, such as the spleen, and fluids will pass from the tissues to restore the normal blood volume. When only small quantities of blood are lost, however, these changes are not marked. Again, the evidence of bone marrow stimulation is not as striking as following acute blood loss, but leukocytosis of the neutrophilic type, an increase in the number of platelets and reticulocytes, possibly polychromatophilia and even normoblasts may appear. The red corpuscles are at first little affected, but later cells smaller than normal and containing less hemoglobin per unit of volume are produced.

When the chronic blood loss has proceeded for some time, changes which are fairly characteristic will be observed. A few corpuscles of normal size and perhaps an occasional macrocyte will be seen, but the predominant cells are small pale red corpuscles many of which are of bizarre forms. Both the mean diameter and the mean volume of the red corpuscles are greatly reduced. Values for mean corpuscular volume as low as 55 or even 50 cubic microns have been encountered (Wintrobe). The quantity of hemoglobin contained in the red corpuscles is diminished even more than the volume of the cells, so that the "concentration" of hemoglobin is significantly reduced, a change which is very characteristic of this type of anemia. Likewise very low values for color index, volume index and saturation index are found (Osgood).

Total bone marrow exhaustion eventually supervenes. Poikilocytes become more numerous. The red corpuscles are mere rings and reticulocytes, polychromatophilia, normoblasts and microblasts are no longer found. Fewer granulocytes are formed and leukopenia may be quite marked. Platelets are reduced in number. The blood plasma becomes colorless and milky white in appearance.

Very occasionally in this form of anemia there may be a superficial resemblance to pernicious anemia. The mean size of the cells may be normal or may even be slightly greater than normal, and the blood smear may show many large corpuscles. The megalocytes of pernicious anemia, however, are not seen and the cells are obviously not well filled with hemoglobin. Very marked differences in size seldom appear and no evidence of hemolysis either in the blood or in the urine or stools is found.

Diagnosis.—The diagnosis depends in most cases on the anamnesis. Evidence of loss of blood should be specifically sought in both the clinical history and the examination. The cause of the bleeding must be discovered and the blood diseases of which the hemorrhage may be a complication ruled out. Excessive menstrual bleeding especially in young adults may be the only symptom of purpura haemorrhagica. In such a case the bleeding time will be found to be greatly prolonged, the blood clot nonretractile, the platelets markedly reduced in number and the tourniquet test often positive.

Treatment.—The treatment entails and prognosis depends upon removal of the cause of the blood loss. In addition to this, successful treatment will depend not only on the measures employed but also on the condition of the bone marrow. If the bone marrow has become exhausted much time and patience will be required. **Rest in bed, in the open air and sunlight, a well balanced palatable diet and larger doses of iron are essential.** At this point the treatment of anemia by means of special diet, organ extracts, iron and various accessory factors may well be discussed.

THE TREATMENT OF ANEMIA

General Measures.—In the treatment of anemia of whatever cause, **physical rest and mental serenity** are fundamental. Rest in bed is very valuable and even a short period of such treatment may be most advantageous. If **fresh air and sunshine** have been lacking they must be supplied as far as possible. A **dry, warm climate** is most suitable for the majority of cases of anemia. As anemic patients are particularly sensitive to cold, **chilling** should be particularly guarded against and avoided. **High altitudes** sometimes prove of benefit through stimulation of the bone marrow. **Massage and hydrotherapy** are valuable adjuncts in treatment but should be used in moderation. As the patient improves in strength and well-being and the blood findings justify it, **exercise** should be assumed gradually and systematically persisted in, but **physical exertion to the point of actual fatigue** should be avoided as far as possible until the patient's health is fully reestablished. Relapse may result from neglect of this simple precaution. In this connection it is important to bear in mind that in all anemias of high degree the cardiovascular system is involved and there is likely to be a peculiar circulatory instability and a greater or less degree of myocardial insufficiency.

The various **gastro-intestinal disturbances** must be treated as they arise and will usually disappear as the anemia is overcome. Many patients suffering from anemia are victims of more or less obstinate constipation, and this may be intensified if iron is employed in the treatment of the case. In the greater number of instances the use of **fruit, vegetables and bran**, either as a cereal or incorporated in bran bread or biscuit, and the **drinking of water** in the early morning hours before food is taken, with a certain amount of instruction given the patient, will suffice to relieve the trouble. It is probable that at least 75 per cent of the cases of constipation are purely due to lack of understanding of the physiologic process, and this statement is especially true of adults and healthy people. In them the rectal reflex may have become so blunted as to render the normal stimulus caused by the descent of fecal matter insufficient to constitute a recognized demand for stool; hence, the value of regularity in going to stool regardless of any demand on the part of the bowel. In the case of walking patients, furthermore, the importance of **assuming a sharply flexed position** of the body so extreme as to bring about the reinforcement of the action of the abdominal muscles by pressure upon the thighs, is not understood sufficiently. Not only does this attitude secure the maximum of reinforcement pressure but it seems to produce a relaxation of the sphincter which is most important and valuable.

If these measures in themselves are insufficient, the various **preparations of mineral oil** may be used for their mechanical effect. Wherever possible constipation should be overcome without recourse to salines or purgative drugs. **Rectal injections of olive oil** (120 to 240 c.c.) at bedtime may be used if needed, but measures such as the **soapsuds enema** should be avoided as far as possible. In the case of bed patients who have to use the bedpan, it is occasionally absolutely necessary to give laxatives, but **manual pressure** such as reinforcement pressure over the abdomen may correct the difficulties encountered.

The management of a case of anemia from the viewpoint of the nervous symptoms differs in no way from the general treatment of nervous conditions, and it is quite permissible as indications arise to use sedatives such as the **bromides**, or barbituric acid preparations such as **barbital, luminal or ipral**. In the

case of the excessively nervous individual under treatment in bed and in the hospital, it is often of special importance and value to administer over considerable periods small doses of the bromides or, better still, divided doses of barbital.

Diet in Anemia.—The investigations of recent years have added much to our knowledge concerning the dietary treatment of anemia. Most noteworthy are the experiments of Whipple, Robschey-Robbins and their coworkers. These investigators produced anemia in dogs by bleeding so extensive and repeated at such intervals that the hemoglobin reserve was exhausted and a very severe anemia produced. These dogs were fed standard bread diets which furnished food requirements sufficient to maintain health for months and years, and yet permitted minimal hemoglobin and red cell regeneration over and above that required to make up for normal cell destruction ("maintenance factor"). In this way a uniform anemia level was maintained and yet a constant and maximal stimulus to the production of hemoglobin was insured. By the addition of other diet factors and drugs to the basal ration of the bread mixture, the influence of these substances on blood regeneration was tested under well controlled experimental conditions.

The results of these experiments, which have been recently reviewed by Robschey-Robbins, are most illuminating and instructive. As is now well known, **liver, kidney and chicken gizzard** were found most efficient in favoring hemoglobin regeneration, whereas dairy products, so much used in dietotherapy generally, were the least valuable. In the accompanying table the relative value of a number of different foods in the treatment of chronic posthemorrhagic anemia in dogs, is indicated. The investigations of Whipple and his associates indicate that, excepting possibly spinach and beet greens, the chlorophyll-containing vegetables, so much vaunted as a source of blood regenerating material, scarcely merit their reputation, whereas **fruits** such as **apricots, peaches and prunes**, and, to a lesser extent, **raisins, fresh grapes and apples**, are of great value.

Minot and Murphy, basing their work on these experiments, have shown the effectiveness of liver in producing in pernicious anemia active blood regeneration, a rapid return to a normal blood picture and the amelioration of the symptoms of this disease. In sprue and in the so-called "pernicious anemia of pregnancy" similar spectacular results have been observed. In other types of anemia the results of this form of treatment have, in comparison, been disappointing. In thrombopenic purpura, sickle cell anemia, aplastic anemia, hemolytic jaundice and the leukemias, liver therapy has not appeared to be of special value.

In the various forms of "secondary" anemia the results of liver therapy have likewise been somewhat disappointing. Whipple has pointed out that in secondary anemia liver has appeared ineffective because insufficient time has been allowed. In pernicious anemia a large store of hemoglobin is present in the body and the effective factor in liver appears simply to render this hemoglobin available. In anemia due to chronic blood loss, on the other hand, the store of hemoglobin in the body may be completely or at least largely exhausted and therefore a much more gradual response is to be expected. Murphy and Powers, Dyke, Vaughan and others have shown that liver, and particularly a combination of **liver and iron**, are of distinct value in the anemia resulting from chronic blood loss. In the chronic obscure anemia observed in women who have followed a faulty diet for many years and perhaps have suffered also from disease of the pelvic organs, generous amounts of **liver, red meat, fruit**, such as **apricots, peaches and prunes**, and **vegetables**, in addition to large quantities of **iron**, have been shown to be of value if continued for several months.

Just on what factors the beneficial effect of various foods depends, is obscure. The opinion expressed by Koessler and his associates and by Simmonds and his coworkers that vitamins play an important rôle in blood regeneration is not borne out by the experiments of others (Sure, Kik and Walker, Cartland and Koch). Butter and cream, which are rich in vitamin A, have been shown to be of no value in blood formation. Whipple has pointed out that the amount of iron in the various foods is not related to the amount of hemoglobin they will

TABLE III
HEMOGLOBIN PRODUCTION AS INFLUENCED BY DIET *

Nature of Food	Diet, Grams daily	Hemoglobin Production (Two-week feeding period) Grams
Animal Organs	Liver, beef, 450	95
	Liver, beef, 300, bread, 300	80
	Liver, chicken, 250, bread, 300	80
	Gizzard, chicken, 250, bread, 200	80
	Kidney, pig, beef, or lamb, 250, bread, 300	70
	Spleen	35
	Pancreas, 250	35
	Uterus, pig	28
	Heart, pig or cattle	25
	Stomach, cattle	20
	Brain, 250	20
	Bone marrow, 35	20
Animal Skeletal Muscle	Pig, 250, bread, 300	30
	Beef, 250, bread, 300	17
Fish	Whale, 250, bread, 300	13
	Meat or liver †	inert
Eggs	Eggs, 150, bread, 300	45
Fruits	Apricots, 200, bread, 300	48
	Peaches, 200, bread, 300	45
	Prunes	40
	Raisins, 200, bread, 300	25
	Grapes, fresh	25
	Apples, fresh or dried	25
	Raspberries, 200, bread, 300	5
	Blackberries	inert
	Orange juice	inert
Vegetables	Spinach, 200, bread, 300	15
	Beet greens	15
	Cabbage (red and white)	10
	Asparagus, 200, bread, 300	9
	Lettuce	9
	Onions, carrots, Brussel's sprouts, parsley, celery, beet tops	inert
Dairy Products	Butter, 100, bread, 350	15
	Cheese, American	15
	Cream, 100, bread, 400	10
	Milk, 450, bread, 400	3
Bread	400	3

produce. Nevertheless, the ash of apricots and peaches is as effective in blood regeneration as are the raw fruits, and therefore Whipple feels that fruits and vegetables are probably valuable because of a combination of minerals and not because of the presence of the chlorophyl nucleus or vitamins.

The beneficial effect of liver does not seem to be due to its content of iron, vitamins or proteins. The extract of liver elaborated by Cohn, Minot and Murphy for the treatment of pernicious anemia is nonprotein in nature, free of carbohydrate, lipoids or iron and is not one of the known vitamins. The effective substance is thought to be a polypeptide or nitrogenous base. According to Dakin, West and Howe, it is a compound of beta-hydroxy-glutamic acid and hydroxyproline. This extract, although as effective in pernicious anemia and sprue as is whole liver, has little effect in other types of anemia. In the pernicious anemia of pregnancy Murphy states that it has little effect. In their anemic dogs Whipple and his associates have found the extract to produce only 10 to 20 per cent of the effect of whole liver. Whipple, Robschit-Robbins and Walden have recently obtained a "secondary anemia fraction" from hog livers which possesses 65 to 75 per cent of the potency of whole liver in experimental

* The values given, which are taken chiefly from the reports of experiments by Whipple *et al.* on dogs, are only approximate and are presented only with the view of comparing the value of different foods in the treatment of anemia.

† Connery has recently reported the successful treatment of pernicious anemia by means of an aqueous extract of fish liver.

hemorrhagic anemia. They suggest that the secondary anemia fraction facilitates more hemoglobin and less stroma formation, whereas the effect of the pernicious anemia fraction is the reverse of this.

With so many problems remaining unanswered, the practical application of the newer knowledge of the value of diet in the treatment of anemia is difficult and remains in many instances a matter of trial and error. It is obviously important that the diet be most carefully looked into, and one must be certain that any deficiency therein is corrected so far as possible. This involves in not a few instances an attempt to correct the ideas of the individual patient with respect to the articles of food which properly enter into a nourishing dietary.

In the case of most individuals, and particularly those treated in bed, it is well to place them upon not less than **six feedings a day** and to make the dietary as **nourishing and simple** as possible, having due regard to the tastes and unavoidable idiosyncrasies of the patient. One frequently encounters an apparent idiosyncrasy with respect to certain articles of food and this should receive due attention and be treated with proper respect. One finds patients demanding at times unusual articles of diet and possessing for these a special craving. This is particularly true of substances containing acids, such as pickles, olives and the like, but the same craving may be manifested for sweets or even more or less bizarre articles as smoked herring, cooked or uncooked; and here again one should be willing usually to **meet the patient's craving** with reasonable and rational indulgence. The articles desired do not necessarily represent any distinct legitimate demand on the part of the body tissues, although in some instances this is the case, but it is certain that by indulging such whims one may often obtain from the patient a willingness to be nourished to a degree impossible if he or she is denied.

All food should be tastefully served and seasoned while cooking. Too great **uniformity and monotony in the meals** should be avoided. There is no reason why **coffee** should be avoided, but **tea** ought not to be taken when iron is being administered. An error occasionally made consists in the overfrequent, untimely and ill-regulated giving of fruits. The best time to take fruit is before breakfast and in general the early part of the day; the worst time, after five o'clock in the afternoon. The excessive ingestion of citrous fruits may produce a troublesome spastic constipation. Instances of this condition have been encountered which were due wholly to the cause stated and not removable until citrous fruit was completely withdrawn or radically limited. **Cooked fruit** may be found to produce less digestive disturbance than raw fruit since the cellulose envelope is broken down by the heat.

In the **administration of liver** it is important to secure adequate dosage and continuous effect. This is best attained by the **daily administration of one-half to one pound of whole liver** until the blood has returned to normal. The response of the hematopoietic organs is best determined by frequently repeated **reticulocyte counts**. In pernicious anemia the magnitude and rate of the reticulocyte response vary with the amount of effective material given and the extent of the bone-marrow hyperplasia. Following the administration of about 300 gm. of whole liver or the corresponding amount of liver extract in this disease and in sprue, the rise in the percentage of reticulocytes begins 3 to 8 days following the commencement of treatment and reaches a maximum 7 to 13 days after the rise has begun. On the whole, the height of the reticulocyte rise varies inversely with the red cell count, the lower the cell count the greater being the percentage of reticulocytes to be expected.

When such great amounts of liver must be given for some length of time it is obvious that much ingenuity as to the method of administration need be exercised. The discovery of an effective liver extract has greatly simplified the treatment of pernicious anemia. Nevertheless, many patients find the cost of the extract prohibitive, especially since it must be taken for an indefinite length of time. Furthermore, some acquire a marked distaste for it. In such cases, as well as in the treatment of other forms of anemia in which liver rather than liver extract is needed, much judgment and indulgence are often necessary in

order to secure the coöperation of the patient. It is wise not to force too much liver at first. It is best to commence with 50 gm. and then to increase the dose. Liver may be administered in any form desired but **prolonged boiling and over-cooking should be avoided.** It should be borne in mind that the factor in liver which is effective in pernicious anemia is water soluble and therefore the watery residue of all liver preparations must be included in the food given the patient. Again, it is important to inform patients that liver loses approximately 40 per cent of its weight when cooked and that this must be allowed for when the daily dose is weighed out. Calves' liver is preferable to beef liver only because it is more tender and less sinewy. Sheep's liver, deer liver or chicken liver may be used for variety. If raw liver is used the possibility of parasitic infection must be borne in mind.

The following recipes are in use at the Johns Hopkins Hospital:

LIVER RECIPES

Broiled liver: Dash liver in hot water, remove skin and broil until done or par-boil in a small amount of mineral oil. Five minutes are generally allowed for cooking. The drippings should be saved and may be served with potatoes or rice.

Ground liver: Broil liver until cooked through and put through a meat grinder, using the finest attachment.

Stuffed tomatoes and stuffed green peppers: Season ground liver with salt, pepper if desired, and moisten with tomato juice or boiled dressing. Stuff this mixture in tomatoes or green peppers and bake. This mixture may also be stuffed in half a baked potato. The potato is cut in half, scraped out and half its contents replaced in one side of the shell, the liver mixture filling the other half.

Liver loaf: Take ground liver and season with salt, pepper and onion, moisten with tomato juice or boiled dressing and cover with buttered bread crumbs, using only one teaspoonful of butter. Bake just long enough to brown the crumbs.

Liver soups: 1. Add finely ground liver to 1 cup of tomato broth (canned tomatoes), put through the sieve and season. Cooked celery may be added to this.

2. Add ground liver to white sauce, using 1 cup of milk, 1 tablespoon of butter, 1 tablespoonful of flour and season.

3. Add ground liver to beef or chicken broth from which all fat has been removed.

Liver pulp: Put raw liver through a meat grinder several times, using the finest attachment. Add enough cold water to the pulp to make it the consistency of heavy cream and strain, using a coarse sieve or potato ricer. Beat up with egg beater and serve ice cold. The preparation may be flavored with fruit juice. If it is preferred, liver pulp may be served warm with bouillon.

Liver juice: Sear liver slightly in a pan for less than a minute. Place the seared liver in a square made of several folds of gauze and squeeze out the juice (about $\frac{3}{4}$ cup juice from 2 lbs. liver).

Jellied liver: Steam liver in chicken broth until soft. Cut up the liver or pass through a strainer. Season with salt and a very little sugar. To 1 quart of chicken broth and liver add 1 tablespoonful of gelatin. Set in molds. Tomato broth may be substituted for chicken broth. The jellied liver may be decorated with parsley or white of egg, and may be served on lettuce.

The following suggestions, made by Nicholls, will be found most useful:

"I. Broil slices of calves' or beef liver.

Do not soak in water first.

(Steam chicken livers.)

II. Remove veins and prepare as one of the following:

A. Chop in small pieces.

B. Mince coarsely.

C. Mince finely and strain.

III. Season with salt and a pinch of sugar.

Moisten with gravy from roast meat, or with broth from broiled meat or fowl.

Additional distinctive seasonings are:

Curry, chop suey sauce, Worcester sauce, tomato purée with chili sauce, celery salt, onion salt, picallili, sherry.

With A, B or C flavored to taste, the following may be prepared:

Hot Dishes

Pie, Cornish pastry or turnover of A or B plus cooked vegetables, covered with or enclosed in a plain pastry crust.

Shepherd's pie or B or C covered with mashed potato and browned in the oven.
 Stuffed vegetables. Tomatoes, green or sweet red peppers, baked potatoes, etc., stuffed with B or C.

Indian curry of B or C with raisins and boiled rice.

Timbale. A mould lined with boiled rice or macaroni and stuffed with B or C. Steam, invert and serve with additional gravy.

Soup. C with addition of chicken or meat broth or milk. To vary add strained tomatoes and chili sauce or boiled rice.

Stew. A or B plus cooked carrots, onion, potatoes, leeks, served en casserole (improved with sherry).

Cold Dishes

Liver in aspic. A, B or C in jellied meat broth or clear aspic jelly.

Liver cream. C set in milk plus gelatin.

Tomato salad. Tomatoes stuffed with C and garnished.

Stuffed egg salad. Hard-boiled egg whites stuffed with C.

Sandwiches. B or C on toasted white or graham bread or crackers.

Club sandwich. B or C on toast with lettuce, tomato, mineral oil dressing, and thin slice of lean boiled ham."

In addition to containing the foods which have been shown to be of great value in hemoglobin regeneration, the diet for the anemic patient should be adequate and well balanced. As a general principle the concentrated carbohydrate foods, such as cakes, pastry, pies, puddings, candies and the like, should be avoided since their ingestion necessarily lessens the appetite for other more valuable foods and furthermore because they favor colonic indigestion. For similar reasons fats should not be used in excess. Nicholls suggests that the liquid diet include orange juice, egg white, coffee with milk, liver pulp, liver milk soup, strained spinach, tomato juice, cereal gruel, tea and strained fruit. For the weak appetite, egg, toast, butter, calves' or beef liver sandwiches, dill pickles, minced liver with macaroni, peaches, raisins, soda crackers, tomato bouillon, and jellied liver in aspic may be given. With increasing appetite, scraped raw beef sandwiches, green peppers stuffed with calves' liver, beefsteak, and baked potatoes stuffed with liver may be added. When the appetite is established, lamb chops, broiled kidneys, liver and kidney pie, and liver club sandwich are suggested.

Iron and Accessory Factors.—Ever since Menghini in 1747 described the presence of iron in blood, this drug has been extensively used in the treatment of anemia. Its use has nevertheless been the subject of much debate not only as regards the proper method of administration but even the effectiveness of this drug has been questioned. In spite of the apparent value of large doses of iron in the treatment of chlorosis, demonstrated by earlier clinicians, the value of iron in the treatment of anemia was not borne out by the earlier experiments of Whipple and Robscheit or by those of Musser. Subsequent experiments by Whipple and his associates in long continued severe anemia produced in dogs by the method already described have, however, quite conclusively shown that the ash of effective foods such as apricots and peaches favors hemoglobin regeneration. These workers attributed these favorable results to the presence of minerals. Subsequent experiments have indicated the value of iron in this type of severe anemia. The experiments of Riecker suggest that the usefulness of iron may be dependent on the depletion or exhaustion of the iron reserve of the body. Whipple has pointed out that it may take months to exhaust this reserve in dogs. The apparent contradiction of the earlier and subsequent experiments reported by Whipple can thus be explained.

Iron is absorbed throughout the entire intestinal tract but probably the duodenum and upper portion of the small bowel are most important. It is carried away either in solution or in the form of fine colloidal particles by the blood and to a lesser extent through the lymphatic vessels. Iron is stored chiefly in the liver. It is not clearly understood in what manner this metal influences hemoglobin formation. It may serve as a direct building stone for hemoglobin. Abderhalden felt that in addition to iron the pyrrole group was necessary for the formation of hemoglobin, and in this way he explained the ineffectiveness of inorganic iron when given with milk as the only food in the treatment of anemia. Many investigators believe that, in part at least, iron acts by irritating the bone

marrow as well as by stimulating the growth and metabolism of other tissues. The increase in the number of reticulocytes which Mettier and Minot, as well as Keefer and his associates observed to follow the administration of iron would suggest such a stimulation of the erythropoietic organs.

Although very much remains to be learned concerning the use of iron in the treatment of anemia, its administration appears to be well substantiated both by experiment and by clinical results in those types of anemia in which the iron reserve of the body and the hemoglobin content of the red corpuscles are reduced. In chlorosis the value of this drug permitted it to be classed almost as a specific. In the anemia resulting from chronic blood loss its use is clearly indicated. In the various types of chronic simple anemia a prolonged trial should be made, the cause of the anemia being of course at the same time sought for and removed. The combined use of liver therapy and iron in many types of "secondary" anemia yields, according to Whipple and to Minot, results which are more favorable than those observed following the use of either of these alone. In pernicious anemia it is difficult to find any reason for the use of iron.

There has been much discussion as to whether iron should be given in organic or in inorganic form (Williamson and Ets), whether the soluble or the insoluble compounds are to be preferred (Mitchell and Schmidt) or whether the ferric or ferrous salts are superior (Simmonds *et al.*). Simmonds, Becker and McCollum found that vitamin E is necessary for the absorption of iron in rats. Whipple and his associates found ferric citrate, ferric or ferrous chloride and ferrous ammonium sulphate equally effective in their anemic dogs. Each of these preparations when given in quantities equivalent to 60 mg. of iron daily had a maximal effect of 50 to 60 gm. of hemoglobin production per two-week period.

It is difficult to derive conclusions applicable to clinical practice from the experiments of the investigators above mentioned. No conclusive evidence has been presented to support the use of one iron preparation in preference to another. Bland's mass, the most commonly used preparation, is not markedly astringent and is usually well tolerated by the stomach. It is important to bear in mind, however, that iron pills may pass through to the stools entirely unaffected by the digestive juices. It is preferable, therefore, to administer the metal as a powder in gelatin capsules, 0.3 gm. (5 gr.) each. They should be freshly made and to insure this may be ordered as follows:

℞ Ferri Sulphatis Exsic.
Sodii Bicarbonatis aa 8 gm.
M. Fiat cap. No. xlviii.

The fresh ferrous carbonate is formed in stomach.

Reduced iron (*ferrum reductum*) is another effective form in which this metal may be administered. It may be ordered as a powder in capsules containing 0.2 to 1 gm. each. It is costly, however, to have capsules made and so it may be found more suitable to order a quantity of ferric ammonium citrate. A teaspoon will hold about 3 gm. of these crystals. They may be taken dissolved in water or milk. If the appetite is poor the tincture of perchloride of iron may be found useful but the preparation should be well diluted and in a syrupy vehicle. A very large number of preparations of organic iron compounds have been put on the market from time to time and many of these are effective, but it may be questioned whether they are any more valuable or as meritorious as the inorganic preparations above mentioned.

Much larger doses than are usually employed should be given. Lindberg and Seyderhelm use *ferrum reductum* in doses of 1 gm. (15 gr.) and then gradually increase this to 3 gm. (45 gr.) daily. The latter represents nine times the customary dose. Likewise Barkan recommends large doses of iron. Schulten has recently reported that favorable results followed the administration of 6 gm. of reduced iron daily in patients in whom smaller quantities (2 gm.) seemed to be ineffective. The experience of Mettier and Minot and of Keefer and his coworkers has been the same. Bland's mass may be given in quantities of 2 gm. (30 gr.) daily, and this amount should be increased until the patient

is taking 4 to 6 gm. of the mass per day. Iron and ammonium citrate may be given in doses as great as 3 teaspoonfuls (9 gm.) per day.

The relatively large doses are usually well tolerated. One preparation may be found satisfactory when another produces nausea or other untoward symptoms.

Iron should be taken after meals in order to avoid any irritating effect on the stomach. Liquid preparations of iron when administered by mouth should be taken through a glass tube, or lacking this, the mouth should be thoroughly rinsed out each time, as otherwise the teeth and tongue will be blackened by decomposition of the iron preparation into the sulphide.

The unabsorbed iron is excreted as the sulphide, darkening the feces. During their passage through the intestine iron salts exercise an astringent action and give rise to constipation. The measures already mentioned in the discussion of the treatment of constipation in anemia may be effective in counteracting this, or it may be necessary to give such drugs as phenolphthalein, rhubarb or cascara sagrada.

In recent years much has been written concerning the value of metals other than iron in anemia. Waddell, Steenbock, Hart and Elvehjem found pure iron ineffective in the treatment of nutritional anemia in rats, whereas commercial iron or the ashed residue from beef liver, lettuce leaves or yellow corn, all of which they found to be contaminated with copper, was of distinct value. Other investigators (Myers and Beard) have attempted to show that still other metals such as manganese, zinc, aluminum, antimony and germanium are of importance, but these contentions have not been substantiated. Whipple and his associates feel that minerals do play a very definite rôle in the regeneration of red cells and hemoglobin in the hemorrhage type of experimental anemia, but have been able to demonstrate only an irregular effect on the part of copper and manganese and no effect on the part of any other minerals. In a number of patients suffering from chronic idiopathic hypochromic anemia, Mills reports benefit from the use of iron and copper in combination when iron alone was ineffective. Likewise Schiff and his associates, as well as Josephs, have reported several cases of anemia in infants in which iron alone was ineffective, whereas when the milk and iron were supplemented with copper improvement followed. These investigators themselves feel that the value of copper as an adjunct to iron has by no means been convincingly proved, but its further trial under carefully controlled conditions seems to be justified.

Arsenic has long been used in the treatment of anemia with the object of stimulating the bone marrow. Its value is nevertheless questionable. In animal experiments Isaacs found that increased delivery of erythrocytes occurred only after the arsenic administered had been eliminated, whereas Whipple and Robschey-Robbins observed no appreciable effect on red cell or hemoglobin production. In the form of Fowler's solution in doses commencing with 2 to 3 drops three times a day and increased until slight symptoms are produced, or injected intramuscularly in the form of sodium cacodylate [0.03 to 0.06 gm. (0.5-1 gr.)] every few days, arsenic may perhaps be given a trial when other measures have failed.

Blood Transfusion in Anemia.—Ever since the discovery of a simple method by which the violent reactions which occasionally followed transfusions could be foreseen and to a very large extent avoided, this procedure has been much used in the treatment of anemia. It has become apparent that the suitable selection of the donor is the prerequisite for the safe performance of transfusion. The donor must be free from infections of any kind. The need for not only serological tests but a carefully taken history to avoid the transmission of syphilis cannot be too greatly stressed.

The methods of determining the group to which the donor and recipient belong and the tests for iso-agglutinins to determine compatibility have already been described (Volume I). Although it is most important that the cells of the donor should not be agglutinated by the serum of the recipient, it is well also, even though in an emergency it is not essential, that the cells of the recipient should not be agglutinated by the serum of the donor. Witts has recently

pointed out that the rule by which Group IV individuals are accepted as "universal donors" is not without exceptions.

The **methods of administration** of the blood may be classed as direct and indirect. **Direct blood transfusion**, which involves the anastomosis of vessels with or without cannula, possesses the disadvantage of requiring much skill and experience and does not permit the operator to know precisely how much blood he is taking or giving. Furthermore, the blood vessels used must be sacrificed. It is a method which is therefore little used now. By the **indirect methods** blood is first withdrawn from the donor and then injected into the patient. Coagulation is prevented by the use of **paraffined apparatus** or **anticoagulants**.

Whole blood transfusion, which is the name given to methods in which no anticoagulant is used and the blood is therefore injected into the patient as nearly unchanged as possible, has long been employed and with the improved apparatus of the present day is gaining preference over all other methods. Among the technics which may be mentioned are (1) the syringe-cannula method of Unger, (2) the Brown-Percy-Schläpfer method (Nather, Ochsner and Boitel), (3) the Jubé apparatus and (4) the Scannell apparatus. The **Percy modification of the Kimpton Brown method** is one of the best since the transfused blood comes in contact with no rubber tubing or air. Its chief disadvantage is that a "team" is required for its performance whereas a single operator can both withdraw and give blood with the Jubé or Scannell apparatus. Disadvantages of whole blood transfusion methods are the necessity for speed and the fact that donor and recipient must be brought together.

Numerous **anticoagulants** have been suggested in an attempt to overcome the serious effects which may follow the injection of blood partially coagulated as the result of imperfectly performed whole blood transfusions. Of these anticoagulants **sodium citrate** is now by far the most popular. The use of citrate greatly simplifies the operation of transfusion. This method (Dutton, Gibson) possesses the important advantages that as soon as the blood is thoroughly mixed with this substance coagulation is prevented and the use of the blood may, if necessary, be delayed for several hours. It may even be transported for long distances. An important disadvantage is the fact that the apparent simplicity of the method breeds carelessness. Furthermore, it has been shown that sodium citrate increases the fragility of the red cells (Drinker and Brittingham), markedly reduces the opsonic index of the plasma and the phagocytic power of the leukocytes, and furthermore destroys complement and platelets (Colebrook and Storer, Agnew).

The **immediate effects** of blood transfusion vary to some extent with the amount employed and depend on the presence of the transfused blood in the vascular system of the patient as well as on the effect of this blood on his tissues. Blood transfusion is followed by an increase in blood volume, a decrease in the rate of blood flow and in the pulse rate and an increase in blood pressure. There is an immediate increase in the quantity of hemoglobin in the blood which is maximal in 24 hours and then falls again, and a somewhat less ready rise in the red cell count. This increase amounts to 500,000 cells per c.mm. or more and is often greater than that which can be accounted for by the number of cells added. There is also an immediate increase in the number of polymorphonuclear leukocytes and platelets. Under favorable conditions the bone marrow is stimulated and this is indicated by a persistence in the increased number of white corpuscles and platelets, already noted, and an increased formation of young red corpuscles. The patient's symptoms become alleviated, there is a sense of well-being and revival of interest in life, increased appetite and other clinical signs of improvement.

The **quantity of blood** used is an important factor in these reactions. Usually 450 to 700 c.c. of blood are given. Large quantities of blood are valuable in increasing the blood volume and blood pressure but are not important in stimulating the bone marrow. As a matter of fact, the reverse of this may occur following very large transfusions as with a state of relative plethora the bone marrow tends to become inactive. Excessively large quantities of blood are dangerous, moreover, on account of the possibility of causing dilatation of the heart

and acute pulmonary edema. An important warning symptom of such an effect is a series of short, sharp coughs. If the transfusion is continued, precordial pain, backache and pain in the legs will follow and finally dyspnea and a productive cough appear.

Blood transfusion is indicated whenever the blood volume need be restored quickly, as in acute posthemorrhagic anemia or when the store of red corpuscles need be replenished. Such a measure is useful, for example, prior to a necessary operation in an anemic patient. In conditions where blood formation is defective, as occurs, for example, in the poisoning which follows the use of arsenic in sensitive patients, such measures may serve to tide the patient over until the bone marrow has recovered its function. In all conditions where an aplasia of the bone marrow appears to be present, **repeated transfusions** should be employed although, of course, if there is total aplasia no lasting benefit will follow. Blood transfusions may often serve to stimulate the bone marrow and here small quantities of blood are more effective than large amounts. In the hemorrhagic diseases the introduction of blood platelets and other substances concerned in blood coagulation is a valuable, even if sometimes only a temporarily effective measure. In hemophilia, purpura haemorrhagica and particularly in hemorrhagic disease of the newly-born, blood transfusions hold a definite place. In the anemia resulting from repeated blood loss, transfusions may so improve the state of the tissues that healing of the bleeding and ulcerated parts will follow and recovery take place.

The transfusion of blood is not devoid of **danger** and should not be undertaken without proper consideration of the risk involved. The danger of infection is obvious. The possibility of the occurrence of dilatation of the heart and acute pulmonary edema, especially where myocardial weakness exists and large quantities of blood are given, has already been mentioned. Witts reports 5 deaths in a series of 3430 blood transfusions given through the Blood Transfusion Service of the British Red Cross Society. These deaths he states were largely due to "inadequate compatibility tests." In such instances where hemolysis actually occurs the reaction may commence after as little as 20 c.c. of blood has been given and is ushered in by restlessness, anxiety, generalized tingling sensations, precordial pain or oppression, dyspnea and acute severe pain in the back. Flushing of the face occurs, and then collapse with cold, clammy skin, feeble pulse, nausea and even vomiting and syncope. In a short time there is a chill, followed by a rise of temperature, nausea, vomiting and delirium. The urine usually contains hemoglobin, and jaundice follows in 24 hours. The severity of these symptoms and the rate at which they develop depend largely on the rate at which the injected cells are destroyed. The majority of these cases recover, but death may ensue early from the circulatory collapse or later as the result of injury to the liver or kidneys.

Simple febrile reactions occur in about 10 to 20 per cent of cases although some operators report as few as 1 per cent. A chill and subsequent fever may follow within an hour after the transfusion or, especially in the blood diseases, these reactions may be delayed for 24 hours. There may be headache, nausea, vomiting, tachycardia and prostration. These reactions are of little consequence aside from the discomfort and anxiety produced. They are not dependent on iso-agglutination or hemolysis. Small thrombi in the transfused blood, excessive alkali or acid in the diluting fluids, new rubber tubing, injury to the red corpuscles by the citrate (these reactions are much more common when the citrate method of transfusion is employed), incompatibility of the white corpuscles (Doan) are some of the factors which may be responsible. Allergic phenomena such as urticaria may occur. Symptomatic measures for the fever, **acetyl salicylic acid** or **codeine** for the discomfort, and, when there is circulatory collapse, **adrenaline** should be employed in the treatment of these reactions.

Transfusions may, if desired, be repeatedly given to the patient from the same donor but it is wise to **repeat compatibility tests** each time. Certain patients tend to react with increasing severity to repeated transfusions. Minot feels that the majority of such cases are examples of the presence of agglutinins in weak titers, the concentration of which is increased as transfusions are re-

peated. Clough points out, however, that such reactions may occur without the presence of demonstrable evidence of cross-agglutination or hemolysis.

The reader interested in a detailed discussion of blood transfusion is referred to the excellent review by Doan.

Splenectomy.—The subject of splenectomy is discussed generally in Volume VIII. The desirability of this procedure in certain types of anemia will be discussed under the diseases in the treatment of which it is sometimes employed.

SIMPLE CHRONIC ANEMIA

Definition.—This is the anemia commonly associated with the majority of infections, intoxications and chronic systemic diseases. The blood picture suggests defective blood formation. Blood loss is not associated nor is there evidence of excessive blood destruction. The anemia is termed simple because there is no very radical alteration from the normal blood picture, and chronic because this type of anemia is usually insidious in its inception and frequently slow in repair.

Etiology.—This type of anemia is usually found in (1) chronic infections, including focal infections, tuberculosis, syphilis, parasitic infestation and, to a less extent, acute infections; (2) chronic diseases, especially malignant disease, gastro-intestinal ailments and diseases of the kidney and liver; (3) intoxications produced by various poisons such as lead, mercury and arsenic; (4) improper food, poor hygienic surroundings, and (5) pregnancy.

Some *chronic infection* difficult to locate and yet far-reaching in its effects is not infrequently the cause of an anemia of this type. *Acute infections* do not as a rule produce anemia at once but, if they are at all *prolonged*, and particularly if nutrition is impaired, anemia soon develops and the renewal of normal hemopoietic activity becomes one of the problems in the treatment of the convalescent. Severe anemia in *tuberculosis* is unusual but a mild simple anemia is not uncommon. Anemia of this type is frequently seen in the secondary and tertiary stages of *syphilis*. Rarely increased blood destruction and greatly disordered blood formation are seen in association with the latter disease. Simple chronic anemia may be associated with infestation by *Oxyuris vermicularis* or *Taenia saginata*. The nature and cause of the anemia associated with hook-worm disease are much debated. Very frequently we have found the blood picture to resemble that of chronic posthemorrhagic anemia with its very small and excessively pale red corpuscles rather than that observed in this type of anemia.

Brown and Roth found no evidence of blood dilution (hydremia) or increased blood destruction in *chronic nephritis* and state that the anemia which accompanies this disease is the result of decreased blood formation. The anemia serves to differentiate chronic nephritis with hypertension from essential hypertension which is unaccompanied by any blood changes.

The influence of diet on blood regeneration has already been discussed. Severe anemia has been produced in laboratory animals by Hart *et al.*, Scott and Barcroft, and others by means of milk and other iron-poor diets. There can be no doubt that an *inadequate diet* will likewise produce anemia in human beings. Particularly is this true of the iron starvation which follows the continued use of a milk diet.

Anemia is frequently observed in *pregnancy*. In the majority of instances this anemia is of the simple, chronic type and is considered by many to be "physiological" (Alder, Pepper). In a painstaking study which consisted in frequent observations on the blood of 15 otherwise healthy pregnant women, Kühnel noted definite reduction in the red cell count, hemoglobin and relative cell volume by the eighth week of pregnancy. The anemia progressed until the sixteenth to twenty-second week when the condition became stationary, usually at a level of 3.5 to 3.75 million red cells, 75 per cent hemoglobin, and 32 to 34 c.c. of packed red cells per 100 c.c. of blood. Frequently temporary decrease in the severity of the anemia occurred about the thirty-second to thirty-fourth week. Recovery took place but slowly after delivery, a normal condition of the blood being attained only after four to six and even twelve months by Kühnel's

patients. A recent study by Bland, Goldstein and First showed that only 3 of 200 pregnant women had red cell counts greater than 4.2 million. Since etiologic factors such as infection and toxemia did not seem to be necessarily associated and, furthermore, since a large proportion of these were private patients living under good environmental conditions, these writers concluded that factors connected with the gravid state must be in some way responsible for the anemia. Hydremia and the demands of the fetus for hemoglobin are perhaps the two most important factors in the production of this physiologic anemia of pregnancy.

The effect of climate, temperature and season on the blood has been recently reviewed by Wintrobe. There appears to be no foundation whatever for the contention that an anemia of purely climatic origin is present in otherwise healthy individuals residing in the South.

Symptomatology.—The anemia produced by these varied etiologic factors may be of all grades of severity. The symptoms and physical findings are those common to anemia together with the symptoms of the associated disease. Increased blood destruction being absent, no icteric tint will be found in the skin and mucous membranes.

BLOOD CHANGES.—The number of red corpuscles and the hemoglobin are reduced, as is also the volume of the packed red cells of the blood. The erythrocytes are, on the average, smaller than normal and contain less than the normal quantity of hemoglobin. The reduction in the size and in the hemoglobin content of the cells are, however, approximately parallel, so that normal corpuscular hemoglobin concentration values are found. The blood plasma is normal in color and shows no evidence of increased blood destruction. Examination of the blood smear reveals anisocytosis, the extent of which varies with the severity of the anemia, and but little poikilocytosis. Few other changes are observed as a rule. Variations in the white corpuscles depend on the nature of the causative factor, whether it is pyogenic infection, tuberculosis or some other disease, as well as on the stage of the disease, a preponderance of multisegmented neutrophils ("shift to the right") and relative lymphocytosis being common when the illness is of long standing and the bone marrow exhausted.

Although the blood findings described are customarily found, it must be borne in mind that all grades of reaction on the part of the hematopoietic apparatus from marked hypoplasia to hyperplasia and evidence of increased blood destruction, may occasionally be encountered. Polychromatophilia may be observed and the percentage of reticulocytes may be increased. In simple chronic anemia such findings are, however, unusual and, should they be repeatedly observed in the absence of any increase in the number of red cells, evidence of blood loss or of some other cause for bone marrow stimulation should be sought. Rarely a blood picture somewhat resembling pernicious anemia is met with.

Diagnosis.—The diagnosis of simple chronic anemia depends on the presence of a blood picture which gives no indication of increased blood destruction or disordered and excessive blood formation, and the discovery of the cause of the anemia. In this type of anemia, its seriousness, as gauged by the number of red corpuscles, is slight as compared with the severity of the symptoms, whereas in an anemia such as pernicious anemia relatively mild symptoms are often encountered in spite of very marked anemia.

Treatment.—In addition to removal of the cause of the anemia, if possible, much effort and patience must be directed to the treatment of the anemia itself if the period of convalescence is to be shortened. A good, well balanced diet which includes adequate quantities of foods such as liver, chicken, gizzard, kidney, eggs, apricots, peaches and prunes, together with sufficient rest and moderate exercise, fresh air and sunshine, larger quantities of iron and an appetizing tonic should all be employed. The type of liver extract which has proved to be so valuable in the treatment of pernicious anemia has little to offer in simple chronic anemia. Much more valuable are whole liver and large doses of iron. The recent report of Mettier and Minot emphasizes the value of large doses of iron in the anemia which is encountered in individuals, chiefly women, who have partaken of a diet consisting chiefly of concentrated carbo-

hydrate food and markedly deficient in animal protein foods, fruits and green vegetables.

Prognosis.—Prognosis naturally depends to a very large extent on the seriousness of the causative factor and the readiness with which it can be removed, but even when this has been done recovery is usually slow. The “physiologic” anemia associated with pregnancy usually clears up after parturition, although this may take several months. It is never necessary to terminate the pregnancy on account of this type of anemia as symptomatic treatment will usually be found quite successful.

SIMPLE ACHLORHYDRIC ANEMIA

An anemia which occurs chiefly in women in middle and later life and which is characterized by an absence of free hydrochloric acid from the gastric juice, frequently glossitis, slight splenomegaly, microcytosis, no leukocytosis but often relative lymphocytosis, no signs of increased blood formation or excessive blood destruction, and with little tendency to spontaneous recovery has been described (Faber, Kaznelson, Watkins, Gram, Witts, Waugh). In addition to the symptoms commonly encountered in anemia, there are those characteristic of achlorhydria such as frequent stool and loss of appetite. Paresthesias due to affection of the posterior columns of the cord may occur. Kaznelson describes typical hollow finger nails which are very tender and brittle. Vesicles with heaped-up white margins may be present on the tongue and stomatitis, particularly at the corners of the mouth, may be encountered. Dysphagia may occur. Kaznelson found a hyperplastic (normoblastic) bone marrow in these cases. However, normoblasts are not frequently encountered in the blood stream.

Simple achlorhydric anemia is readily distinguished from pernicious anemia by the differences in the blood picture. Banti's disease is differentiated by the absence of jaundice, hematemesis or ascites. From chlorosis Witts distinguished simple achlorhydric anemia by its later occurrence, the presence of glossitis, and its frequent association with and aggravation by pregnancy. Simple achlorhydric anemia is uninfluenced by liver therapy or hydrochloric acid, but large doses of iron are strikingly effective. The observations of Mettier and Minot that iron is more potent for blood formation when absorbed from an acid than an alkaline medium within the intestinal tract suggest the possibility that long continued achlorhydria may be causatively associated with iron deficiency and consequent anemia even when the diet has not been faulty. Gram and Witts have pointed out the common occurrence of simple achlorhydric anemia and pernicious anemia in the same families.

CHLOROSIS

Definition.—Chlorosis is a disease of unknown causation occurring in young females, characterized by a pronounced anemia of a hypoplastic, hemoglobin-deficient type, as well as by an almost specific favorable response to the internal administration of iron.

Etiology.—Ordway and Gorham state that this disease was first described by Ashwell in 1836, although there is little doubt that it was known long before. Because of its occurrence, practically exclusively, in women during the period of sexual development, namely, between the ages of 14 and 25, it has been assumed by many that the blood changes result from some fault of function in the glands of internal secretion. Naegeli attributes the disease to ovarian insufficiency.

There is another large group of observers who attribute the anemia to faulty personal hygiene and nutritional insufficiency. The frequency with which chlorosis was observed in girls whose idiosyncrasies as to diet included the avoidance of meats and the frequently exclusive subsistence on sweetmeats and other highly concentrated carbohydrate foods, as well as in those whose circumstances did not offer adequate diet, is pointed to as significant in any consideration of the cause of this disease. Greene stressed the fact that many of the patients he observed were young female immigrants who, coming from an open country life

with coarse wholesome food and abundance of outdoor work, had exchanged these favorable conditions of environment for city living, domestic service, work in public laundries and other occupations of a relatively unfavorable nature.

Naegeli calls attention to the heavy bony framework, the large thorax and the tendency to excessive fat of the subjects of this disease. In Greene's experience nearly all of the cases of pronounced chlorosis occurred in individuals of the congenitally asthenic (universally visceroptotic) type. Numerous other factors have been mentioned as being concerned in the causation of chlorosis, such as heredity, psychoneurasthenic states, worry and mental depression, homesickness, lovesickness, as well as constipation and auto-intoxication, tuberculosis and concealed septic foci.

In a disease of this type it is difficult to separate cause and effect. There is little doubt that chlorosis occurred in families. Tuberculosis was frequently associated but it may well be asked which disease predisposed to the other. When examined from this standpoint the evidence relating all these factors to the etiology of chlorosis becomes very questionable.

A most interesting fact which concerns the etiology of chlorosis is the very striking decrease in the incidence of this disease in all civilized countries in the past 25 years. The statistics gathered by Campbell, Cabot, von Hoesslin, Ordway and Gorham, and others are most convincing in this respect. There is no doubt that improved methods of diagnosis have made it possible to eliminate a large number of conditions which were grouped as chlorosis in the nineteenth century. Nevertheless, there is no doubt that there were many cases which could not have been eliminated in this way.

It has been stressed that the disappearance of chlorosis coincided with a period characterized by greatly improved living conditions and the general use of a diversified diet containing, particularly, a large quantity of fruit. Yet, it has been asked, why has chlorosis not reappeared in the European countries where the ravages of war caused the return of all the environmental and nutritional disadvantages which have been said to favor the development of this disease? The absence of chlorosis in spite of these circumstances all the more suggests that, whether nutrition and environment are important or not, the comparatively vigorous, healthful life, no longer encumbered by constricting dress, which so many young women of this day follow, no matter what their station in life, is largely responsible for the disappearance of chlorosis.

Symptomatology.—The onset is gradual, usually extending over a period of several months, but in rare instances chlorosis develops somewhat acutely. Because of its gradual onset, the disease usually has reached a somewhat pronounced stage before any symptoms are noted on the part of the patient, the family or the physician. The history of the patient usually reveals the presence of certain of the contributory etiologic factors already discussed, such as faulty nutrition, overwork and the like.

Few diseases of the blood give rise to a greater number and variety of symptoms than does chlorosis. One of the earliest symptoms complained of usually is loss of energy, and with this goes unusual fatigability. Disturbances of sleep, nervous irritability, deficient mental application and headache are all very common.

GASTRO-INTESTINAL DISTURBANCES are very frequent in chlorosis and are chiefly those falling under the head of gastro-intestinal neuroses. Capriciousness of appetite and sometimes marked abnormalities associated with craving for unusual or even disgusting articles, together with flatulence, heart-burn, vague and often shifting and irregular epigastric distress after meals, hunger pain and the like are some of the prominent features. Constipation is a troublesome and relatively constant symptom.

As might well be expected, **DISTURBANCES OF MENSTRUATION** are extremely frequent. These may take the form of late appearance of the periods, dysmenorrhea, menorrhagia or, more often, deficiency and irregularity in the flow.

CARDIOVASCULAR SYSTEM.—Arrhythmias are common and are usually of the simpler forms; tachycardia is a common symptom and may be more or less persistent or most troublesomely recurrent; dyspnea on exertion is an almost in-

variable symptom in any marked case of chlorosis and may be attributable either to the condition of the blood alone or to an accompanying circulatory insufficiency with or without actual dilatation of the heart. Edema of the ankles and, less frequently, puffiness of the face are clinical signs of importance frequently present in the more marked grades of chlorosis. The superficial fat is usually rather well preserved.

PALLOR is the most striking outward symptom of chlorosis. In certain instances the skin, and especially the face, is said not only to be pallid but to show the greenish-yellow tint which has given the disease its name (green sickness). However, by far the larger number of chlorotic patients show simple pallor. In some cases one may be entirely misled by the presence of a rosy color in the cheeks and a vivid red in the lips. In these "rosy chlorotics" the presentment of robust and ruddy health may be quite great until the mucous membranes of the pharynx and gums and the ocular conjunctivae are examined. There the presence of pallor is readily noted.

BLOOD CHANGES.—The outstanding feature with respect to the blood findings in chlorosis is the decided poverty of the individual erythrocyte in hemoglobin. The blood appears pale macroscopically, is thin, and the specific gravity, of course, is low. The hemoglobin content of the blood is distinctly reduced while the red cells are not decreased proportionately. Not infrequently normal, or even high normal, values for number of red cells may be found in spite of marked reduction in the hemoglobin. An erythrocyte count under 2 million is rare. The volume of packed red cells is reduced below normal. Consequently mean corpuscular volume and volume index will be found well below normal and very low values for corpuscular hemoglobin and color index are characteristic. The latter may be even as low as 0.3.

Stained specimens show red corpuscles which are smaller than normal and unusually pale (achromia). Marked variation in the size of the cells is unusual and poikilocytosis is rare and never extreme, but may be observed in certain recurrent cases of unusual chronicity and severity.

Polychromatophilia and nucleated red cells are seldom found, but such evidence of bone marrow activity may become marked following effective therapy. No significant changes in the leukocytes have been consistently recorded in early cases, but in the old, long-standing cases leukopenia may be present. The blood platelets are frequently increased in number.

In following the blood changes in this disease it is important to bear in mind that as improvement takes place the number of red corpuscles increases more rapidly than the hemoglobin and the former may have reached normal or above when the hemoglobin is still quite low.

The investigations of Haldane and of Plesch indicated that the total blood volume in chlorosis was increased, but these results have been challenged and Minot has even expressed the opinion that the blood volume is reduced in this disease. Accurate information in this respect would be most valuable in the study of the pathologic physiology of this disease.

Diagnosis.—The first attack of chlorosis practically always occurs before the age of 25 years. After this time a diagnosis of chlorosis must be made with very much hesitancy. Under any circumstance careful search must be made for the presence of focal infections, tuberculosis, renal disease, thyroid disturbance, hookworm infestation and other diseases which frequently produce the symptoms described. Particularly is this caution necessary at the present time when chlorosis is so extremely rare. Again, it should be borne in mind that gastric ulcer is peculiarly frequent in chlorotics and consequently one should not hold too lightly symptoms which might readily be interpreted as purely nervous. In all cases a careful anamnesis and physical examination are indispensable if serious error is to be avoided.

The moderate reduction of the red cell count and the markedly low hemoglobin, the absence of great variations in the size and form of the red corpuscles with the prevalence of small, hemoglobin-poor cells, together with the absence of evidence of active erythropoiesis or cell destruction are features which greatly resemble the findings in the anemia resulting from chronic blood loss. In the

latter condition, however, poikilocytosis may be quite marked whereas in chlorosis this is unusual. Nevertheless it is important to make a careful search for evidence of blood loss. From simple chronic anemia, both chlorosis and chronic posthemorrhagic anemia are distinguished by the more than proportional reduction in hemoglobin.

Complications and Sequelae.—By far the most serious complication of chlorosis is the impermanency of cure so frequently encountered as a result either of lack of persistence on the part of the physician or oftener because of failure on the part of the patient to carry out instructions. Gastric ulcer has been frequently described as a complication of chlorosis, and there is also in this disease a special tendency to thromboses of the sinuses and veins. Again, as in any severe anemia, a certain amount of myocardial weakness and relative insufficiency is present and in many instances there exists an actual dilatation of the heart and secondary edema of the cardiac type. Many of the symptoms of chlorosis which are so readily attributed to the blood condition are actually cardiac in origin, representing a loss of myocardial reserve due to deficient blood supply and the resulting tonus impairment. In cases where exertion dyspnea with or without edema has been present in marked degree, these symptoms do not disappear *pari passu* with the improvement of the blood condition, the myocardial insufficiency being relatively laggard, as might be expected.

Treatment.—The general and dietetic measures already described in the discussion of the treatment of anemia in general are all important in the treatment of chlorosis. The striking benefit which follows the administration of large doses of iron is now a matter of common knowledge. The importance of rest may be stressed. If the hemoglobin is less than 60 per cent, a period of rest in bed of usually three weeks' duration will be required. Measures must be taken to overcome the dislike for meat which is so common among chlorotics or to provide suitable substitutes. Frequent small meals are recommended in overcoming the perversities of appetite shown by these individuals.

Treatment must be persisted in until the hemoglobin as well as the number of red cells has returned to normal. Frequent reexamination is advisable because of the great tendency to relapse in this disease.

Prognosis.—In cases of primary chlorosis, properly treated, the prognosis is good and recovery should take place in practically every instance. In actual practice, for reasons already stated, a considerable number of the primary cases do not result in complete recovery and some of these become and remain chronic. There can be no doubt that the persistence of blood impairment in any individual is an invitation to disease, both acute and chronic, and constitutes a persisting impairment in the general health which may lead to breakdown or be embraced in the term "chronic invalidism." A great number of women carry mild and even relatively severe grades of anemia all their lives.

Death does not result in any instance from chlorosis itself though it may occur by reason of a coexisting gastric ulcer or the development of sinus and venous thrombosis.

Pathology.—Little is known concerning the pathology of chlorosis. Minot states that hyperplastic bone marrow has usually been found.

APLASTIC ANEMIA

Synonyms.—Aregenerative anemia (Pappenheim), toxic paralytic anemia (Schneider), hypoplastic anemia (Sheard).

Definition.—This term is applied to a group of anemias which are characterized clinically by a progressive and frequently fatal course and pathologically by deficient or totally absent blood formation.

Etiology.—An idiopathic and a secondary type of aplastic anemia are distinguished. SECONDARY APLASTIC ANEMIA may arise in one of the following ways:

(1) *Chronic intoxication with chemical poisons.*—These include arsenical compounds, benzol, trinitrotoluol and colloidal silver. Krumbhaar has described such a condition following certain forms of gas poisoning.

Although in comparison to the wide use of *arsenic* and its compounds depressed bone marrow function as the result of the use of this drug is very rare, an ever-increasing number of cases is being reported. This subject has recently been reviewed by Farley. The untoward results do not seem to follow the use of any particular arsenical compound but are probably associated with special susceptibility on the part of the patient, perhaps congenital weakness of the hematopoietic tissue. Not only is aplastic anemia occasionally produced by the use of these compounds, but purpura haemorrhagica, marked granulocytopenia with anginal symptoms and the like have been described as following its use, indicating thus an occasional selective toxicity or, rather, special susceptibility on the part of some component of the bone marrow tissue. Moore and Keidel caution that itching, a mild macular, papular or vesicular rash, prolonged fever or malaise, or any tendency towards purpura in a patient who has received arsphenamine, should arouse suspicion and is sufficient cause for thorough examination of the blood. Farley points out that the arsphenamines are formed by the substitution of arsenic in the benzol ring and suggests that the direct causation of the blood dyscrasias produced is the disintegration *in vivo* of the arsphenamines, thus permitting a benzol-like action to take place.

In 1897 Santesson first described fatal poisoning and anemia in 4 girls who had worked in a tire factory where *benzol* was used as a solvent for rubber. Selling in 1910 reported fatal aplastic anemia resulting from chronic benzene poisoning in 3 girls working in a tin can factory. Bone marrow stimulation with final exhaustion has been produced experimentally in benzol-poisoned animals by Selling and by Hurwitz and Drinker. The subject of benzol poisoning as an industrial hazard has been discussed by Hamilton, McCord and others. Dry cleaners, feather workers, milliners, printers, tanners, workers in rubber industries, tanners, varnish and paint workers, gilders and coke-oven workers are mentioned by Graham-Rogers as possible subjects of benzol poisoning.

The granular white corpuscles are most susceptible to the influence of benzol, the red corpuscles the least vulnerable, while the platelets take an intermediate position. The red corpuscles may be affected by the hemorrhage associated with platelet involvement and purpura; acute hemolysis may occur, or true aplastic anemia may result, either primarily or as a consequence of exhaustion following hemorrhage or hemolysis.

(2) Excessive exposure to *roentgen rays* and *radio-active substances* may result in severe and even fatal aplastic anemia. That a truly aplastic anemia does not always follow poisoning by these substances, however, appears from Martland's study of individuals engaged in painting luminous watch dials. The blood of five of these individuals showed large cell anisocytosis, megaloblasts, leukopenia, but, it is important to note, no bilirubinemia. A dark red marrow was found throughout the femurs.

The effects of roentgen rays on the blood have been studied by Isaacs and by Minot and Spurling.

(3) Occasionally severe, *overwhelming infections* have caused aplastic anemia. This has been observed following pneumonia, typhoid fever and diphtheria. Marrow necrosis has been produced experimentally with diphtheria toxin (Duke).

(4) Aplasia of the bone marrow may be the terminal stage of pernicious anemia, myeloid leukemia, tapeworm anemia, severe chronic posthemorrhagic anemia and some myelophthisic anemias. An aregenerative or hypoplastic anemia is frequently associated with Banti's disease.

IDIOPATHIC APLASTIC ANEMIA was first described by Ehrlich in 1888. The disease occurs in young adults, chiefly between the ages of 15 and 30 years. Its causation is entirely unknown but, since the subjects not infrequently give a history of preceding pallor of long duration, a congenitally defective bone marrow has been suggested as a predisposing factor. There is no adequate reason for considering this disease a form of pernicious anemia, as has been proposed. The fever and rapid course of idiopathic aplastic anemia suggest infection of some type as an etiologic possibility, the toxic agent having special affinity for blood-forming tissues.

Symptomatology.—The onset of aplastic anemia is insidious. In the secondary forms symptoms may develop three weeks to several months following exposure to the causative agent. Progressive weakness preceded by fatigability is usually the chief complaint or at best one of the outstanding features of the history. Other symptoms common to anemia such as those referred to the cardiovascular system and disturbances of menstruation are frequently present. These patients are unusually susceptible to sepsis and therefore fever is frequent and some complicating infection may be found. Symptomatic purpura haemorrhagica with epistaxis and bleeding from the mucous membranes is almost always present. The patient is pale, sometimes strikingly so, and this pallor may be a trifle waxy in appearance. The yellowish tint of pernicious anemia is wholly lacking. Petechiae in the skin or buccal or pharyngeal surfaces are common. The spleen is not palpable. Except for extreme pallor or petechiae, the tongue is normal.

BLOOD CHANGES.—The striking feature of the blood in aplastic anemia is the presence of red corpuscles which are quite normal in appearance, particularly in view of the severity of the anemia. The red cells are reduced in number and this reduction becomes rapidly more marked. The reduction in hemoglobin and in the volume of packed red cells is proportional so that normal values for corpuscular volume, corpuscular hemoglobin and corpuscular hemoglobin concentration are found. The volume, color and saturation indexes are usually about normal if accurate methods for their determination are employed. If, however, hemorrhage has been a factor contributing to the anemia, the hemoglobin content of the red cells is reduced.

The erythrocyte count is often as low as 2,000,000 or less when the patient is first observed. Marked leukopenia is the rule and very low platelet counts yield further evidence of defective bone marrow activity. As already mentioned, poikilocytosis and anisocytosis are slight or wholly absent. All forms of nucleated red cells are absent or extremely scant. Such evidence of activity as polychromatophilia or the presence of reticulocytes is rarely observed and, in total aplasia, is of course absent.

Of the white corpuscles those formed in the bone marrow are affected almost entirely and the leukocytes which are found are chiefly small lymphocytes. The latter usually make up 70 to 90 per cent of the leukocytes present.

The bleeding time is prolonged and the blood clot is nonretractile. Coagulation time is usually normal. In this disease, as in some instances of purpura haemorrhagica, the resistance of the red cells to salt solution is peculiar in that complete hemolysis occurs in a solution of higher strength (often 0.36 to 0.38 per cent sodium chloride) than is normally required. This may perhaps be interpreted as pointing to a lack of young red cells.

OTHER LABORATORY FINDINGS.—Gastric secretion is normal or only slightly diminished as a rule. No evidence of increased blood destruction is found in the blood plasma, urine or stools.

Diagnosis.—The absence of signs of active, though disordered, blood formation such as marked aniso- and poikilo-cytosis, various forms of nucleated red corpuscles, polychromatophilia, Cabot rings, Howell-Jolly bodies, reticulocytes, and the marked reduction in the total number of red and white cells, the disappearance of granulocytes and the low platelet count, at once indicate markedly defective blood formation.

An aplastic stage of pernicious anemia is usually ruled out by the lack of a characteristic anamnesis, the absence of such characteristic features as tongue and neurological signs, and the want of any evidence whatever of hemolysis. Furthermore, even in the aplastic state a number of abnormally large erythrocytes will be encountered in most instances of pernicious anemia, while in other types of aplastic anemia such cells are not found. Other forms of secondary aplastic anemia must be ruled out by specific enquiry concerning any of the possible etiologic factors.

The resemblance of aplastic anemia to idiopathic purpura haemorrhagica is usually great because of the presence of purpura, thrombocytopenia, prolonged

bleeding time and nonretractile clot in both conditions. The anemia in the latter disease, however, is of the posthemorrhagic type and extreme leukopenia is rare.

In the various forms of granulocytopenia ("agranulocytosis") reduction in the number of red corpuscles or platelets is absent or, at most, not marked. Occasionally acute leukemia in the nonleukemic phase may be encountered. In such cases a distinction can usually be made because of the presence of immature leukocytes.

A final diagnosis of idiopathic aplastic anemia frequently cannot be made until all forms of treatment have proved to be of no avail and the autopsy findings confirm the clinical diagnosis.

Treatment.—Every attempt should be made to find and if possible remove the cause of the anemia. In the case of chemical poisoning, the illness itself serves to remove the patient from the source of trouble. As has already been mentioned, treatment by means of any of the arsenical compounds should at once cease on the appearance of any of the premonitory symptoms described.

In the treatment of the anemia itself absolute rest and intelligent feeding are primarily essential. Of all measures available for the treatment of anemia, frequently repeated transfusions are by far the most promising in this disease. In the secondary types of aplastic anemia repeated transfusions, by providing the patient with fresh blood which contains the leukocytes and platelets he so much needs, even though the life of the corpuscles introduced be very brief, may serve to check bleeding, aid bodily resistance and supplant the bone marrow until such a time as the paralyzed hemopoietic organs recover.

Prognosis.—In the idiopathic form of aplastic anemia, the course is progressively, inexorably and more or less rapidly fatal. Death ensues in the course of a few weeks although life may linger as long as six months. In the secondary forms the outcome depends on the possibility of removing the cause, the degree of damage done, the mode of treatment employed, the success with which complications such as pneumonia are prevented and the patient's own power of recovery. Although the fate of many cases of secondary aplastic anemia is the same as that of patients suffering from the idiopathic form, no measures should be neglected in the attempt to bring about recovery.

Pathology.—Autopsy, which alone makes possible a positive diagnosis, reveals hypoplasia or complete aplasia of the bone marrow. Only yellowish-white fat is seen in the marrow cavities and on microscopical examination the marrow is found to be made up chiefly of fat, fibrous tissue and lymphocytes. In rare instances small foci of hyperplastic marrow may be found and cases have been described in which a hyperplastic bone marrow was found in spite of a totally aplastic blood picture. In such instances we can only infer that there has been some disturbance in the mechanism of red cell delivery.

The spleen is fibrous, the malpighian corpuscles small and the cells of the pulp scanty.

MYELOPHTHISIC ANEMIA

This is a form of anemia due to the mechanical limitation of hemopoietic tissue through invasion of the bone marrow by pathologic tumors or tumor-like formations such as myeloma, chloroma, myeloid leukemia, lymphatic leukemia and metastases of hypernephroma or carcinoma. Osteosclerotic anemia, which arises in a similar manner to the anemia here described, is caused by the addition of new bone to the preëxisting osseous structures and consequent encroachment on the bone marrow.

The blood picture at first usually gives evidence of intense stimulation or irritation of the bone marrow. Anisocytosis is marked, there are many macrocytes, and nucleated red corpuscles are very numerous. Most of the latter are normoblasts but younger and more abnormal forms may be observed. The irritation of the leukoblastic tissue is indicated by neutrophilic leukocytosis and the presence of myelocytes and even myeloblasts. The platelets may be increased in number or markedly reduced. Minot cites a case of metastatic hypernephroma in which there were very few platelets even though the red corpuscles were not very greatly reduced in number. In explanation of this apparent

paradox he points out that the life of platelets is much more brief than that of erythrocytes, and furthermore, that there is probably more erythropoietic tissue than platelet-forming tissue.

Following the period of irritation of the bone marrow, crowding out of the hemopoietic tissue follows and the condition not infrequently terminates as an aplastic anemia. Prior to complete exhaustion, the embryonic sources of blood formation, such as the liver and spleen, may become active with the result that most bizarre blood pictures may be observed.

PERNICIOUS ANEMIA

Synonyms.—Primary anemia, Addisonian anemia, Biermer's anemia.

Definition.—Pernicious anemia is a chronic disease of unknown causation characterized by achlorhydria, certain gastro-intestinal and neurological disturbances, a progressive course interrupted by periods of remission and relapse, a characteristic response to certain forms of therapy and an anemia of which the chief features are perverted hemogenesis, macrocytosis and hemolysis.

Etiology.—Despite the consistent effort to discover the cause of pernicious anemia, this remains a subject about which we know very little. The connection of certain factors to the etiology of this disease, however, seems to be well established.

GEOGRAPHIC DISTRIBUTION.—Pernicious anemia occurs in all countries of temperate climate but is relatively rare in the subtropics and tropics. In these regions a severe anemia which is indistinguishable morphologically from pernicious anemia is not infrequently seen in sprue. Although extensive studies concerning the geographic distribution of pernicious anemia have not been reported, the data available suggest that there is a marked variation in the incidence of pernicious anemia even within the temperate zone, certain localities furnishing a very large number of cases whereas other regions appear to be quite immune (Cornell, Montgomery, Wintrobe). The variation may be related to differences in soil, as suggested by Montgomery, or may depend on racial and hereditary influences.

AGE.—Pernicious anemia is a disease of late adult life, being most frequent above the age of 40. It is relatively rare under 35 years and extremely unusual in children.

SEX.—In the United States and in England males are attacked more frequently; in Germany and the Scandinavian countries, more women than men have been recorded as suffering from this disease.

RACE.—The disease is common in the Nordic races. Hunter has pointed out that the disease is rare in Jews. Pernicious anemia is not as common in pure negroes as it is in the white race, although its rarity has probably been overestimated. It is said to be uncommon in Orientals (Morris).

HEREDITY. FAMILY PREDISPOSITION.—There is an ever-increasing number of reports concerning the incidence of pernicious anemia in brothers, sisters and other blood relatives (Meulengracht, MacLachan and Kline, Carey, Conner). Of still greater interest is the fact that achlorhydria has a distinct tendency to occur more frequently among blood relatives of patients who have pernicious anemia than among other individuals.

PERSONAL FACTORS. INDIVIDUAL SUSCEPTIBILITY.—If there is one fact that can be considered established concerning pernicious anemia, it is that *achlorhydria* is an almost invariable accompaniment of the disease. Very few exceptions to this rule have been recorded. The more recent investigations concerning gastric secretion in which improved methods of examination such as histamine stimulation and alcohol test meals have been employed, indicate that true achlorhydria is rarely found except in association with pernicious anemia or carcinoma of the stomach (Keefer and Bloomfield). This fact is particularly significant because the achlorhydria is not influenced by remission whether this be spontaneous or induced by liver therapy (Johansen). It has been suggested that the achlorhydria is the result of the disease rather than a predisposing cause. The fact that the lack of free acid has been observed to exist in some

cases for years prior to the onset of any anemia suggests, however, that this abnormality is a manifestation of some predisposing abnormality.

As long ago as 1855 Addison noted that "the disease occurs in patients of a somewhat large and bulky frame and with a distinct tendency to fat formation." Further observations, particularly those of Draper, reveal the fact that the victims of pernicious anemia usually possess a short, broad face with the eyes set far apart, a short, deep chest with wide costal angle, gray or white hair which has turned so prematurely, and are also apt to have blue or light-colored eyes. Males may show a eunuchoid broad pelvis and abnormal distribution of hair.

Pernicious anemia appears to make no distinction between rich and poor, city or country dweller, luxury or filth, occupation, over-exertion or other similar factors, which, it may be noted in passing, are so important in the incidence of many infectious diseases.

PATHOGENESIS.—The facts presented concerning the incidence of pernicious anemia suggest that a distinct predisposition on the part of certain individuals to pernicious anemia is present. Several other observations which bear on this point may be mentioned here.

A condition which very closely simulates pernicious anemia has been observed in individuals infected with the broad tapeworm, *Bothriocephalus latus*. However, in the Scandinavian countries where infestation with this parasite is very common, anemia of the pernicious type has been observed in only about 0.5 per cent of those harboring this organism. The question naturally arises whether some other factor than the parasite is not necessary to produce the anemia (see p. 843).

Piney's studies of the bone marrow in pernicious anemia lead him to believe that there is in the victims of this disease a developmental defect by which there is inadequate development of adult (normoblastic) bone marrow and a compensatory hypertrophy of fetal (megaloblastic) bone marrow. Through the action of some exciting cause which may be the broad tapeworm, syphilis, pregnancy or that which causes pernicious anemia, the signs and symptoms of pernicious anemia are produced.

The etiologic relationship of gastric abnormality to pernicious anemia has frequently been denied because pernicious anemia has not been observed to follow gastrectomy. However, the majority of gastrectomies reported have been incomplete. In Finney and Rienhoff's collection of 9 operations in which the stomach was totally removed, pernicious anemia developed in 2 cases.

The remarkable results produced by the administration of liver and liver extract suggest a "deficiency" of some substance necessary for normal blood formation. Apparently it is possible by feeding liver and other effective substances not only to cause a remission in pernicious anemia but also to maintain, perhaps indefinitely, a normal state. This response is quantitative. It appears that the response to liver medication depends rather on the total amount of active liver principle used during a certain period of time than on the amount consumed each day (Minot, Riddle and Sturgis).

The nature of the action of liver and other effective substances is not understood. Whipple expressed the opinion in 1922 that in pernicious anemia there is faulty blood construction and not increased disintegration. Peabody observed that in relapse there is little tendency in the bone marrow to differentiate mature cells. He suggested that in liver there is some substance which is necessary to promote the development and differentiation of mature red corpuscles.

Castle's recent experiments emphasize again the etiologic relationship of gastric abnormality. This worker found that muscle meat digested by normal gastric juice has the same effect as liver when fed to the victims of pernicious anemia. This effect is not due to either muscle meat or gastric juice alone but is dependent on the interaction of these two substances. Castle's later experiments indicate that the substance in gastric juice which acts upon beef muscle in such a manner as to produce the "effective factor" is neither hydrochloric acid, rennin nor pepsin. These experiments suggest that the absence of hydrochloric acid from the stomach of pernicious anemia patients is not in itself harmful but is rather an indication that some other necessary substance, pos-

sibly an enzyme, secreted by normal gastric mucosa is likewise absent. The presence of free hydrochloric acid in spite of the presence of a pernicious anemia-like blood picture, as is seen in sprue and in very rare cases of true pernicious anemia, therefore does not negate the hypothesis that some abnormality in the secretion of the stomach is related to the development of pernicious anemia. In Castle's words, "The development of the disease is dependent upon an inadequate gastric digestion of protein, thus permitting the development of a virtual deficiency in the face of a diet adequate for the normal man." The value of the extract of desiccated hog stomach developed by Sturgis and Isaacs, with Sharp, may depend on the interaction of normal hog gastric mucosa and the protein of the stomach wall; but Sturgis has recently stated that the active material must be generated in the gastric mucosa and diffuse into the muscle, for either muscle or mucosa alone is effective in producing a remission. The relation of the effective factors derived from the stomach and the liver and kidney is not known.

Although the gastric abnormality which Castle has shown to exist in pernicious anemia is quite clearly related to the changes in the blood, no adequate explanation for the changes in the spinal cord has as yet been offered. These cord degenerations cannot be explained as being caused by the anemia in itself, for in a number of instances neurologic changes have been known to precede the onset of anemia. Mellanby, on the basis of his observations of the influence of vitamin A in protecting the spinal cord of dogs from the degenerative effects of ergot, has suggested that in pernicious anemia there are two deficiencies, namely, a defect in a water-soluble factor which controls the formation of red cells and is contained in aqueous extracts of liver, and secondly, a fat-soluble factor, vitamin A, which controls the nervous system.

The relation of pernicious anemia to the metabolism of fat has attracted the attention of many investigators. The remarkable preservation of fat and the nature of the changes in the nervous system may be cited as evidence indicating such a disturbance. That such a hypothesis must still be borne in mind, even in the light of recent investigations, is suggested by the recent report by Muller that in typical cases of pernicious anemia in marked relapse the blood cholesterol rises suddenly at the onset of the remission, a rise which is "concomitant with the response of the reticulocytes and as a rule is proportional to the intensity of the remission and of greater magnitude the lower the red blood cell count."

THE EXCITING CAUSE.—Though the recent investigations clear up some questions concerning the etiology of pernicious anemia, many still remain unanswered. What actually precipitates the symptoms of pernicious anemia? How are the characteristic periods of remission and relapse to be explained? Why should there be glossitis and neurologic changes?

That some toxin is at work in pernicious anemia is suggested by the wide distribution of the areas affected and the similarity of the changes present in pernicious anemia to those observed as the result of the action of known toxins such as has been reported occasionally in poisoning by saponin, phenylhydrazine, radio-active substances, benzol, and in tapeworm infestation, syphilis and pregnancy. This conception has been recently supported by the observation that the serum of pernicious anemia blood is toxic and inhibits the growth of seedlings (Macht, Tschérkes). Upjohn and his associates, however, could not confirm these results.

Ever since William Hunter in 1888 expressed the view that oral sepsis is most likely responsible for pernicious anemia, a search has been maintained for some specific etiologic agent. A large number of organisms have been mentioned, particularly *Bacillus welchii*, *Bacillus coli* and a streptococcus. Hurst and Knott have postulated the theory that the absence of acid in the stomach permits the entrance and growth of organisms in the small bowel and that toxins are thus produced. Seyderhelm, among others, has reported the production of a pernicious anemia-like condition as the result of the experimental stenosis of the ileum of dogs, and many investigators have reported the production of an anemia similar to pernicious anemia by the experimental introduction of *B.*

welchii toxins (Torrey and Kahn, Nye, Reed, Orr and Burleigh, Nyfeldt, Cornell).

It is difficult although not impossible to explain the results of liver therapy on an infectious basis. Such an hypothesis is, however, certainly questionable in view of the singularly quantitative nature of the response to liver therapy in pernicious anemia. Furthermore, Davidson and Knott have shown that the intestinal flora is unchanged after liver therapy.

A more complete discussion of the etiology of pernicious anemia will be found in the monographs of Cornell, Piney and Davidson and Gulland, and in the papers of Krumbhaar, Means and Richardson, and Wintrobe.

Symptomatology.—The original description by Addison of a patient suffering from pernicious anemia is so clear and accurate that, as a tribute to its author and as an example of the value of clinical observation, it may well be quoted:

"The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse perhaps large but remarkably soft and compressible, and occasionally with a slight jerk, especially under the slightest excitement. There is an increasing indisposition to exertion with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface presents a blanched, smooth and waxy appearance; the lips, gums and tongue seem bloodless; the flabbiness of the solids increases; the appetite fails, extreme languor and faintness supervene, breathlessness and palpitation being produced by the most trifling exertion or emotion; some slight edema is probably perceived about the ankles. The debility becomes extreme; the patient can no longer arise from his bed; the mind occasionally wanders; he falls into a prostrate and half torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of perhaps several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect."

MODE OF ONSET AND INITIAL SYMPTOMS.—The onset of pernicious anemia is usually so insidious that the anemia may be well marked when the patient first presents himself. The chief exceptions to this rule are those instances in which neurologic changes occur before anemia develops or becomes marked.

The initial symptoms are very varied and may suggest the presence of some digestive disorder, cardiac or renal disease, nervous or psychic disturbance, syphilis or even genito-urinary disease or infection. The diagnostic triad, weakness, sore tongue and numbness or tingling, as the first presenting symptoms are rather the exception than the rule. Common initial complaints, in order of frequency are fatigability, weakness and faintness, numbness, tingling and stiffness, headache, nausea, lack of appetite, vomiting, dizziness, dyspnea, palpitation, diarrhea, loss of weight, pallor, abdominal pain and sore tongue. Such symptoms may date back for many months or for several years in their milder degrees, but seldom have been sufficient to attract serious attention save during the few months preceding the oncoming of more serious complaints.

OUTWARD APPEARANCE OF THE PATIENT.—Little can be added to Addison's description just quoted. The superficial fat is usually well preserved until very late in the disease, and the skin, peculiarly velvety and smooth, presents the delicate lemon or grapefruit yellow tint which is so prominent an outward sign of the fully developed disease. Since this characteristic color is largely dependent on the severity of the anemia, the hemolysis of the blood and the presence of subcutaneous fat, it must be borne in mind that it will not be invariably present and may wax and wane with the periods of relapse and remission.

The patient not infrequently possesses the wide face, light-colored eyes, blond or prematurely gray hair, broad chest with wide costal angles and wide pelvis described by Addison and by Draper. There may be evidence of weakness, dyspnea on exertion and exhaustion.

A brownish pigmentation of the skin, diffuse or blotchy, and calling to mind Addison's disease was described by the older writers. This pigmentation may have been the result of arsenic therapy. Petechiae in the skin are unusual.

BODY TEMPERATURE.—Fever of several degrees and irregular in type may not unusually be present. This is often, though not invariably, associated with periods of excessive blood destruction.

ALIMENTARY SYSTEM.—Sore tongue occurs at some time in at least 50 per cent of the cases of pernicious anemia. The tongue symptoms occur more often early than late in the disease and usually become less frequent as the anemia increases. They are associated at their height with a sensation of soreness or rawness, particularly with regard to the taking of food which is hot or sharp in any way. The tongue, in patches or the whole dorsum, at this time appears "beefy" red and there may be shallow white ulcers at the tip and edges. Severe pain may be present. Symptoms are usually marked for a few days and then gradually disappear. After a varying number of attacks which recur at intervals of several weeks, months or years, there is left behind the atrophied epithelium devoid of papillae and the smooth glazed tongue of the declared condition. Actual partial loss of taste may occur.

Less frequently the entire mouth and throat may be extensively involved in a similar manner, causing the patient to complain of burning and pain on swallowing. The teeth are frequently in poor condition and pyorrhea alveolaris is common.

Complaints referred to the gastro-intestinal tract may suggest the presence of a large variety of diseases. Anorexia, nausea, "gas," a sense of fullness and epigastric discomfort, heart-burn, vomiting and irregular abdominal pain varying in intensity, all may occur. Diarrhea occurs at some time in about 50 per cent of cases but there may as likely be constipation. Not unusually the patient may state that there is a semisolid bowel movement immediately on arising and perhaps another or more later in the day. Gastro-intestinal symptoms may be present even 10 years before the patient is outspokenly sick.

Attacks of paroxysmal abdominal pains resembling the gastric crisis of tabes sometimes occur. Such an attack, when associated with vomiting and some abdominal rigidity in a patient who is extremely pale may lead to a mistake in diagnosis. Some of these instances of severe abdominal pain may be related to changes in the spinal cord, but it is interesting to note that similar attacks which have not infrequently been mistaken for an abdominal emergency occur in sickle cell anemia. The relation of these attacks of pain to periods of excessive hemolysis is worthy of speculation.

The liver, particularly in the later stages of pernicious anemia when fatty degeneration and hemosiderosis are marked, may be found to be slightly enlarged. The spleen is moderately increased in size in about 40 per cent of cases and may be palpable. Decided enlargement is unusual.

Although it is generally stated that there is no loss of weight in pernicious anemia, considerable loss occurs in about 40 per cent of cases. Emaciation, however, is rare and, it is important to note, any existing weight loss may be wholly or in large part regained in periods of remission.

CIRCULATORY SYSTEM.—General symptoms such as vertigo, tinnitus, palpitation, dyspnea, sensations of extra beats and excessive weakness and fatigue have already been mentioned. All fatal cases of pernicious anemia are associated with a fatty degeneration of the heart which may reach the most extreme type, and in many instances this results in an enlargement of the heart and marked atonicity and loss of contractility which, together with the diminished hemoglobin and total blood volume, account for the extreme prostration so often encountered in these cases. Cardiac irregularity seldom occurs. In pernicious anemia, as in extreme degrees of anemia from whatever cause, the actual rapidity of the blood stream is greatly increased, the heart muscle is badly nourished, tends to become atonic and the same condition is doubtless reflected in the great vessels. Furthermore, the specific gravity of the blood is lowered decidedly. Thus we find present just the conditions which might produce bruits and these are invariably present. They are usually soft in quality, though occasionally harsh, almost invariably systolic in time and maximal in the great majority of the cases at the second left (pulmonary) interspace.

Systolic bruits may also be heard over the aortic area and at the apex, and

in a very few instances a diastolic aortic murmur has been present during life, obviously due to dilatation of the aortic ring as no changes were demonstrable at autopsy. The vessels of the neck may be seen to pulsate if the anemia is severe and a loud venous "hum" is often heard. The heart rate is slightly increased (80 to 100 beats per minute). The blood pressure is more commonly low in pernicious anemia than in tuberculosis (Lerman and Means).

Cardiac pain similar to that typical of angina has been observed in 3 (Willius and Giffin) to 20 per cent (Coombs) of cases. It has been suggested that such symptoms are the result of anoxemia of the myocardium.

Slight edema about the ankles is often present. Less frequently the face and body may become edematous and even pulmonary congestion and edema, and hydrothorax may occur.

NERVOUS SYSTEM.—The association of anemia with combined degeneration of the cord was first noted by Lichtheim in 1887. Since that time changes in the nervous system have come to be considered a part of the disease pernicious anemia. The frequency of destructive lesions in the nervous system in pernicious anemia is disputed, Woltman finding these to occur in 80 per cent of cases, while Drinker considers that only 30 per cent develop actual cord degeneration. Such differences of opinion are based largely on the interpretation of the meaning of various physical signs and symptoms. It is generally agreed that 70 to 80 per cent of pernicious anemia patients have complaints at some time referred to the nervous system.

Nervous symptoms are nearly always present past the age of 55 and are less common in younger patients. Cord changes and neurologic complaints may precede the development of anemia, and such a diagnostic problem may occur not unusually in younger individuals. Marked remissions in the blood and general condition may occur with little or no alteration in the nervous disturbance.

Subjective sensory disturbances constitute the earliest and most frequent evidence of involvement of the nervous system. Weakness, numbness, pricking sensations in the legs and arms, delayed sensation as in tabes, headache, irritability, lack of concentrating power, dulness, drowsiness, depression, delusions, hallucinations, tinnitus, blurring of vision, girdle sensations and later loss of sexual power may be complained of.

The neurologic changes may be most marked in the posterior columns of the cord, in the lateral columns, in the peripheral nerves, or occasionally cerebral involvements may be more prominent. Thus there may be the predominantly *ataxic type* resembling tabes with difficulty in walking, absent knee or ankle jerks, hypotonicity, disturbance in sense of position and of vibratory sense. On the other hand, the *lateral columns* may be chiefly involved with resulting spasticity, especially of the legs, exaggerated reflexes, hypertonicity and positive Babinski. *Multiple peripheral neuritis* is present in at least 4.9 per cent according to Beigler and Reese and is evidenced by numbness, impaired sensation, paralysis and muscular atrophy.

Frequently neurologic disturbances are of the "mixed" type presenting signs of involved posterior and lateral columns as well as of peripheral nerves. Loss of vibratory sense is frequent and early, as is also loss of discrimination between two points. Sphincter control may be lost in the later stages of the illness. Due to atrophy of the tongue speech may be disturbed.

Mental symptoms are not infrequent but it is usually considered that major psychoses are predisposed to rather than a part of the disease pernicious anemia.

Disturbances of the special senses may occur in the form of tinnitus and disturbance of vision. Optic atrophy or neuritis and retinal hemorrhages may occur.

GENITO-URINARY SYSTEM.—Genito-urinary complaints are rarely primary. There may be symptoms suggesting nephritis which actually is present in the later stages of pernicious anemia and is probably a consequence of suboxidation and the irritation produced by the deposition of iron pigment (Stieglitz).

LABORATORY FINDINGS.—*The Blood.*—Cabot has remarked that in no other disease is the red cell count so often found below 2,000,000 at the first examination of the patient. Marked reduction may occur, counts as low as 138,000

(Naegeli) and even 86,000 (Zadek) having been recorded. Hemoglobin and volume of packed red cells are reduced but not in proportion to the reduction in the number of red corpuscles, thus indicating an average increase in the volume and hemoglobin content of the red corpuscles in this disease. These variations may be measured quantitatively by the calculation of corpuscular volume, corpuscular hemoglobin and corpuscular hemoglobin concentration, or volume index, color index and saturation index as described in Chapter II, this section.

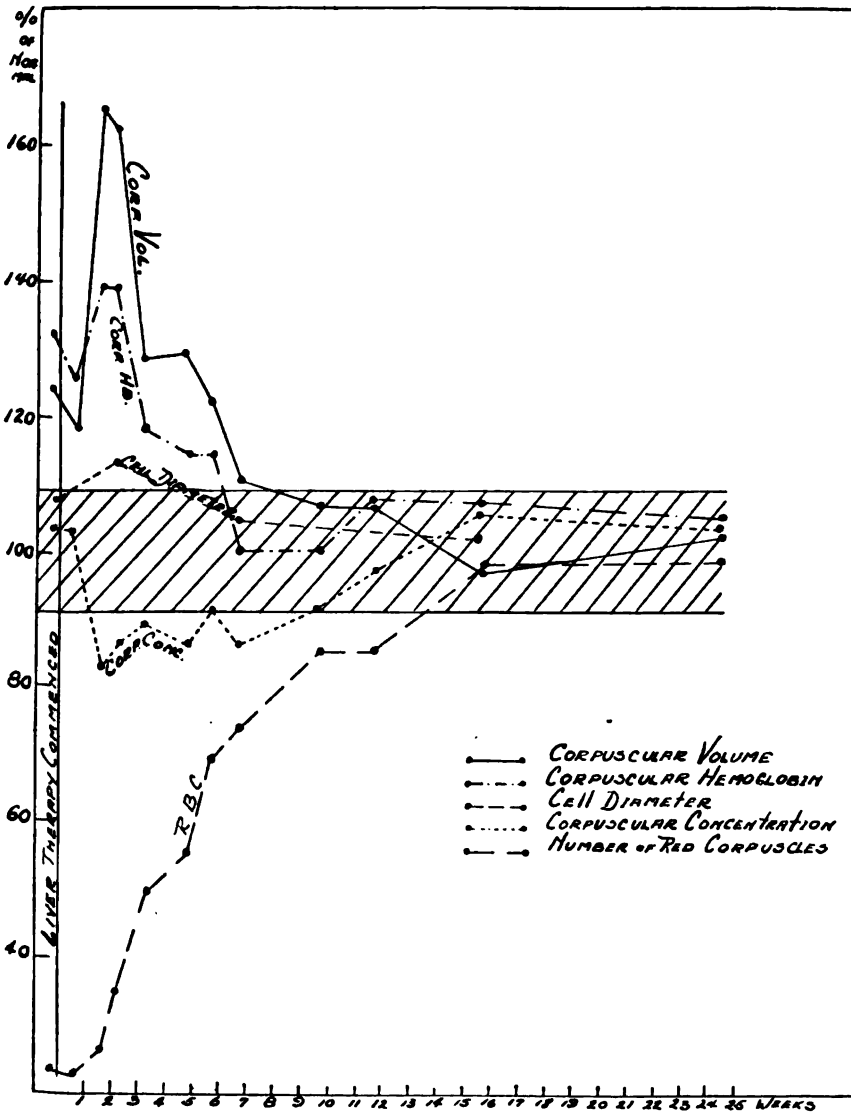


FIG. 29.—VARIATION IN THE MEAN SIZE AND HEMOGLOBIN CONTENT OF THE RED CORPUSCLES ASSOCIATED WITH LIVER-INDUCED REMISSION IN A CASE OF PERNICIOUS ANEMIA. THE NORMAL RANGE OF VARIATION OF ALL CHARACTERS, EXCEPT MEAN CELL DIAMETER, IS INDICATED BY THE SHADED AREA. (Wintrobe, Am. J. M. Sc.)

The mean corpuscular volume is greater than normal in pernicious anemia during the stages of relapse and incomplete remission. Values as high as 164 cu. μ have been observed. Under liver therapy there is a gradual decrease in the volume of the cells and at the time of complete remission normal values are

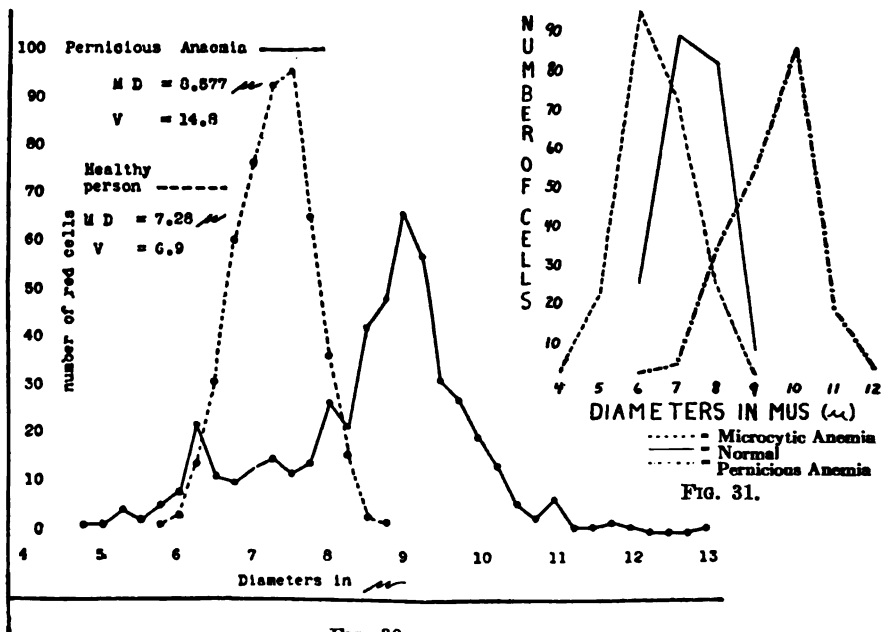


FIG. 30.

FIG. 30.—CURVES INDICATING THE DISTRIBUTION OF VARIATION IN THE DIAMETERS OF THE RED CORPUSCLES IN HEALTH AND IN A CASE OF PERNICIOUS ANEMIA IN RELAPSE. MD IS THE MEAN DIAMETER OF THE RED CELLS, V THE COEFFICIENT OF VARIATION OR DEGREE OF ANISOCYTOSIS. (Price-Jones, Guy's Hosp. Rep.)

FIG. 31.—COMPARATIVE SIZE OF RED CELLS IN MICROCYTIC ANEMIA, NORMAL BLOOD AND PERNICIOUS ANEMIA. (Musser and Wirth, Ann. Int. Med.)

found. Preceding this decrease in mean volume there may be a preliminary increase which probably denotes the disappearance of smaller, fragmented cells (Fig. 29). Similar changes in volume index occur.

In view of the inaccuracy of the commonly used methods of hemoglobin estimation, too great reliance should not be placed on color index in the diagnosis of this type of anemia. Volume index or mean corpuscular volume calculations will be found much more accurate and dependable. When accurate methods of hemoglobin estimations are employed, high values for color index and mean corpuscular hemoglobin are noted. This does not signify, as is rather generally presumed, that the red corpuscles are supersaturated with hemoglobin in pernicious anemia but, rather, that they contain more than the normal quantity of hemoglobin. This increased content of hemoglobin is generally equal to or slightly less than the increased size of the cells, so that their concentration or saturation with hemoglobin remains normal or is slightly less than normal. This is denoted by the finding of normal or slightly low values for saturation index or corpuscular hemoglobin concentration. Along with the gradual reduction in the mean size of the corpuscles during remission there is a similar reduction in the amount of hemoglobin they contain. Not infrequently, during the stages of very active blood regeneration, corpuscular hemoglobin concentration is reduced but returns again to normal as erythropoiesis becomes less rapid (Fig. 29).

C. P. V.—Musser & Wintrobe, Figs. A and B.



Fig. A.—Pernicious anemia (Wright's stain). $\times 950$. The red cell count was 585,000 per c. mm., the mean corpuscular volume 112 cubic microns. *a*, Normocyte, *b* and *c*, macrocytes, *b* being diffusely basophilic; *d*, punctate and diffuse basophilia; *e*, megaloblast; *f*, red corpuscle with Cabot ring body and fine "chromatin dust"; *g*, "giant" multilobed neutrophil.

PLATE V

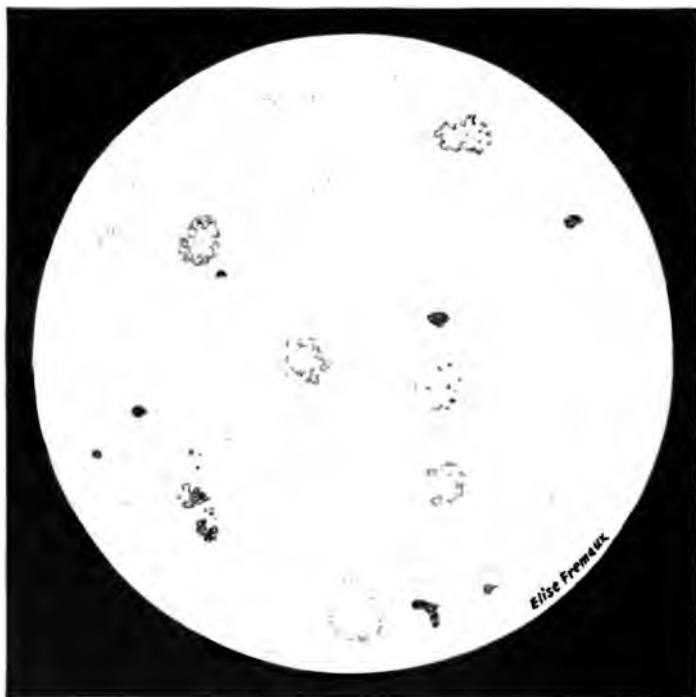


Fig. B.—Pernicious anemia. Stained with cresyl blue in addition to Wright's stain to show reticulocytes. The red cell count was 1,790,000 per c. mm. and the reticulocytes 20 per cent.

Examination of the blood smear reveals the presence of red corpuscles of all shapes and sizes. As Minot has stated, all the abnormalities of red corpuscles may be observed in pernicious anemia excepting achromia. The blood picture depends obviously on the severity of the anemia and the nature of the bone marrow activity, whether hyperregenerative, sluggish or aplastic. Large round or oval macrocytes and megalocytes are typical of this type of anemia. Such cells stain dark red, not because of supersaturation with hemoglobin but because of increased thickness. Some of these cells may show polychromatophilia, thus indicating immaturity. Besides these cells, corpuscles of normal size and even the smallest of microcytes may be observed. Cells shaped in the form of dumb-bells, anvils, cocked hats and many other bizarre forms will also be noted (Plate V, Figs. A and B). Measurement of cell diameter gives objective evidence of the wide variation in the size of the red corpuscles and the average increase in diameter. Although the latter is usually significantly greater than normal in the stages of relapse, this is not always true and, as Price-Jones has stated, "An excessive variability is even more constant in pernicious anemia than a high mean diameter" (Fig. 30).

Polychromatophilia, basophilic stippling, Howell-Jolly bodies, Cabot rings and chromatin particles may all be observed. The significance of all these findings has already been discussed in an earlier chapter and need not be again considered here.

Megaloblasts and macroblasts will be found in pernicious anemia blood, but as a rule these are not very numerous. During the so-called "blast crises" normoblasts appear.

Leukopenia is the rule in pernicious anemia, white cell counts of 4,000 to 5,000 being most common. There is relative lymphocytosis and absolute as well as relative decrease in the number of granulocytes. Occasional myelocytes may be observed in spite of a general "shift to the right" with the presence of numerous multilobed polymorphonuclear neutrophils. Eosinophils are reduced during relapse and their reappearance is a favorable indication. These cells may become very numerous after raw liver has been taken for several weeks (Meulengracht and Holm). Basophils disappear in relapse and monocytes are diminished in number. During remission the white corpuscles may increase in number to reach normal values or higher.

The blood platelets are decreased in relapse and increase in number during remission but rarely regain normal values. Their number serves as an important index of bone marrow activity.

When the bone marrow becomes exhausted there may be a striking variation from the typical blood picture of pernicious anemia and that characteristic of aplastic anemia may be closely simulated. Even under such circumstances, however, the macrocytes and megalocytes so characteristic of pernicious anemia will usually be observed.

Bleeding time is usually normal in pernicious anemia unless the platelets are greatly reduced in number. Coagulation time and prothrombin time may be normal or slightly delayed. The resistance of the cells to hypotonic solutions is usually normal but may be slightly increased.

The brownish-yellow color of the blood plasma in pernicious anemia during the stages of relapse is very striking and serves as an important index of excessive blood destruction. This color in the absence of evidence of obstructive jaundice serves to differentiate hemolytic types of anemia, of which pernicious anemia is the most important representative, from simple chronic anemia, post-hemorrhagic anemia and aplastic anemia (see Plate II). The color is due to the presence of excessive quantities of bilirubin in the blood plasma. Its intensity may be measured by the icterus index test. Normal values for the latter are 5 to 6 units. In pernicious anemia values ranging from 8 to 20 units are commonly observed. The van den Bergh test serves to differentiate this hemolytic type of jaundice from the obstructive variety. In pernicious anemia a positive indirect result is obtained by this test.

The total blood volume in pernicious anemia is reduced, but the reduction concerns the cells only since the total plasma volume is normal or greater than

C. P. V.—Musser & Wintrobe, Figs. A and B.

normal (DeWesselow, Rowntree, Brown and Roth). Ashby noted that low blood volumes were associated with marked symptoms which might be temporarily relieved by such measures as transfusion.

Urine.—The specific gravity is usually low and may be fixed. The color may be pale, but at times of excessive hemolysis it may be brown. Urobilinogen and urobilin excretion is greatly increased during relapse. Albumin is often present in small amounts and there may be a few hyaline and granular casts. There is often an increase of the night over the day volume of urine and in long standing cases there may be other evidence of chronic nephritis.

Stools.—The character of the stools is variable, but wherever there are direct gastro-intestinal disturbances and especially active hemolysis one is likely to find that the stool carries a peculiar chrome (brownish-yellow) color. In certain instances the bowel disturbance may be so great as to lead to an erroneous diagnosis of ulceration of the bowel, or the mucus content may be so high as to suggest the presence of mucous colitis. There is frequently in pernicious anemia a marked increase in the urobilin content of the stool. This may be as great as 3 to 10 times the normal.

Gastric Analysis.—The constancy of achlorhydria has already been commented upon in discussing the etiology of this disease. In the presence of acid in the stomach the diagnosis of pernicious anemia must be made with much hesitation. In examining a patient for achlorhydria it is advisable, if no acid is found, to inject 0.5 c.c. of a 1/1000 solution of histamine hydrochloride (0.5 mg.) subcutaneously to determine the presence of true achlorhydria. In many instances acid will appear on such stimulation in 30 to 55 minutes. In pernicious anemia acid does not appear even after the injection of histamine (Gompertz and Cohen). The total secretory volume is low and the pH of the gastric contents is high (Keefer and Bloomfield).

Diagnosis.—When a patient who is pale presents himself with symptoms of weakness and excessive fatigability; or anorexia, sore tongue or indefinite gastro-intestinal disturbances not related to meals or time of day; or with palpitation, dyspnea or other cardiac symptoms; perhaps with various paresthesias, ataxia or other symptoms referable to the nervous system; particularly when such symptoms date back for months or years in their milder degrees, pernicious anemia should be suspected and a full blood count as well as a gastric analysis should be carried out. If the case is one of pernicious anemia, achlorhydria, which persists even after histamine stimulation, will be discovered and the blood almost invariably will show the presence of large dark round or oval red corpuscles and numerous smaller and misshapen ones. Unless the method of hemoglobin estimation is a good one, the color index determination will be of little value, but the volume index or mean corpuscular volume should be calculated. In pernicious anemia both of these values will be higher than normal and the blood plasma in the hematocrit will be brownish-yellow in color. The white corpuscles and platelets will be found reduced in number and probably lymphocytosis will be noted on the differential count. Physical examination may reveal some of the characteristic features of pernicious anemia, such as the color, the tongue and the neurologic findings, or will indicate the cause of the symptoms complained of. In all such cases a stool examination should be carried out and a search made for occult blood and the ova of parasites. A blood Wassermann, spinal fluid examination, and gastro-intestinal barium series may be needed to rule out diseases which occasionally produce the blood picture of pernicious anemia.

Not only are many of the chronic systemic diseases such as cardiovascular and gastro-intestinal ailments and nephritis, as well as various nervous disturbances such as tabes dorsalis and disseminated sclerosis, frequently confused with pernicious anemia, but occasionally endocrine disturbances and such diseases as typhoid fever, tuberculosis and subacute bacterial endocarditis may need to be differentiated. This is readily done by examination of the blood. Besides these ailments, however, there are several conditions in which there may be close resemblance in the blood picture to that seen in pernicious anemia, and these therefore will not be easily ruled out by the blood examination. These in-

C. P. VI—Musser & Wintrobe, Figs. A and B.



Fig. A.—Normal blood (Wright's stain). $\times 950$.

PLATE VI



Fig. B.—Sprue of moderate severity (Wright's stain). There is marked general macrocytosis. The red cell count was 3,050,000 per c. mm. and the mean corpuscular volume 117 cubic microns.

clude the various forms of aplastic anemia already discussed and the acute and chronic hemolytic anemias which will be described. Among the latter may be mentioned the acute hemolytic anemias resulting from septic causes and those arising from poisoning by phenylhydrazine, acetanilid, benzol or other chemicals; and chronic hemolytic anemias such as are occasionally associated with carcinoma, pregnancy, the parasite *Diphyllbothrium latum* and syphilis. The differentiation of these conditions will be discussed subsequently.

In tropical, subtropical and even occasionally in temperate climates, the differentiation of *sprue* and pernicious anemia is frequently very difficult. The resemblance between these two conditions is so close that many observers have suggested that they are different forms of the same disease or at least have a very closely related etiology (Elders, Musser). The presence of marked gastrointestinal symptoms with diarrhea, bulky, foamy and fatty stools, and emaciation suggests *sprue* rather than pernicious anemia. Paresthesias may occasionally be present but objective signs of neurologic changes are very unusual in *sprue*. Ashford found that considerable anemia was present in not more than one-half of the clinical cases of *sprue*, and he has had several cases of severe *sprue* with practically no anemia. When, however, anemia is present and this is of the macrocytic form, it is quite frequently difficult, if not impossible, to distinguish *sprue* by the blood examination from pernicious anemia. The response to liver therapy in the two diseases is identical (Porter and Rucker, Wintrobe). The chief interest in distinguishing the two diseases depends on the fact that acid is present in the stomach in 50 to 75 per cent of the cases of *sprue*. However, since Castle's work suggests that achlorhydria is an indication of a defective gastric secretion rather than an important factor in itself, this distinction between pernicious anemia and *sprue* may be an unimportant one.

Complications.—It is difficult to deal with the complications of pernicious anemia formally, for these seem to be not so much complications as accompaniments and mere coincidences. Fever, relatively intractable vomiting and diarrhea, spinal cord changes, extreme cardiac weakness and uremic manifestations from decided kidney involvement are the chief complications encountered in this disease. There are no sequelae in pernicious anemia.

Treatment.—The treatment of anemia has already been fully discussed earlier in this chapter. The general and dietetic measures there detailed should be rigidly followed in the treatment of pernicious anemia.

Certain liver extracts have been prepared which have been shown to be as effective in the treatment of pernicious anemia as is whole liver itself, although they appear to be of very little value in the treatment of microcytic types of anemia. These include the **liver extract of Cohn** and his associates (marketed as Liver Extract No. 343, N.N.R.) which has already been discussed, and also those of **Collip**, and of **Porter** (E 29). During the stages of relapse it is recommended that 3 to 6 vials of the Cohn extract be administered daily, or 90 c.c. of the Porter extract. These may be given in water, orange juice, ginger ale, chocolate or other similar vehicles. If the patient cannot swallow the extract it may be administered by stomach tube. Large quantities of extract (20 vials), administered in this way, have been shown by Riddle and Sturgis to cause a reticulocyte response in 48 hours. Pulfer and Reznikoff have recently reported on the successful administration of liver and liver extract per rectum. It is important in employing various extracts of liver to use only those which have been adequately tested for potency.

Sturgis and Isaacs, Sharp, Conner, Snapper and Dupreez, and Wilkinson have all reported favorably on the treatment of pernicious anemia by means of **desiccated hog stomach**. The extract used by Sturgis and Isaacs (ventriculin) is followed by a hematopoietic response similar to that of liver. It is a substitute which will be welcomed by some patients as it is said to have practically no taste. Fifteen to 30 gm. are given daily.

A difficulty which not infrequently arises when liver extracts are used for the treatment of pernicious anemia is their cost, which may prove quite a drain on the patient or his family. Castle and Bowie have recently described a method for preparing a liver extract in the home which is entirely satisfactory. It may

C. P. VI—Musser & Wintrobe, Figs. A and B.

be emphasized that liver extracts possess no advantage over whole liver as regards their effect on the treatment of pernicious anemia except in those cases in which the various protein constituents of whole liver may be considered harmful. Therefore in most instances where cost is an important factor, whole liver should be recommended. The many ways in which it can be prepared make it possible to administer liver in a very palatable and varied manner. Furthermore, it has been suggested that liver rather than liver extract is of value in relieving the neurologic symptoms of pernicious anemia and this gives further support for the administration of some whole liver in all cases, a step which Minot recommends.

Innumerable reports testify to the effectiveness of liver therapy in pernicious anemia. The reports of Ordway and Gorham, Isaacs, Sturgis and Smith, Richardson, Seyderhelm and Schilling may be cited as representing results in large series of cases. The administration of liver is followed in a few days by increased appetite and a sense of well-being. Gastro-intestinal symptoms usually clear up in one or two weeks and dyspnea readily disappears. Tongue soreness usually is relieved but occasionally it may persist. Isaacs has pointed out that in the second week of treatment the pads of the fingers and palms, the chin, cheeks and tip of the nose become flushed. These he attributes to a vasomotor phenomenon. The creases in the palms of the hands do not, however, take on their red color until the blood count approaches $2\frac{1}{2}$ to 3 million red blood cells per cubic millimeter. Weakness and edema are relieved more slowly. The eventual recovery of the heart depends on the degree of fatty degeneration which has resulted from the anemia.

The effect of liver appears to be such as to cause the blood to return to normal and thus relieve the symptoms which are directly and indirectly attributable to the anemia. It must be borne in mind that in tissues where reparative processes do not take place or, at least, are slow, the symptoms and signs resulting from such tissue injury will to a large extent remain. This is particularly true of the nervous symptoms of pernicious anemia. The increased tone of the muscles which follows the disappearance of the anemia permits activity in cases where the patient has been completely bedridden. Where the neurological disturbances are peripheral in character much improvement may be expected. Once the abnormal reflexes indicate that degenerative changes have taken place in the cord, perfect restoration of function cannot be expected. We have observed coördination improve, paresthesias diminish or disappear, vibratory sense increase and sphincter control improve. There are a number of favorable reports (Sturgis, Isaacs and Smith, Bubert, Blaschy, Ungley and Suzman, Baker *et al.*), and the remarkable improvement observed in some cases is sufficient ground for a hopeful outlook in all instances. **Passive and active movement, massage, dry heat and reëducation** will be found important adjuncts in treatment.

The simplest and most valuable manner in which the effectiveness of liver therapy may be determined is by means of the **reticulocyte count**. The technic for carrying out such counts is so simple that they should not be neglected. In 3 to 5 days following the administration of liver the reticulocytes commence to increase in number. The height of this rise varies inversely with the red cell count, being greatest when the red cell count is low. In such instances reticulocyte counts of 30 per cent or more at the end of 10 to 14 days of treatment are commonly observed. When the red cell count is 3,000,000 or higher the reticulocyte response is slight. The red corpuscles increase in number following the increase in reticulocytes, and as the red cells become more numerous the reticulocytes diminish rather rapidly, so that, even in severe cases, there will frequently not be more than 1 to 3 per cent at the end of 15 to 20 days of treatment.

Along with the reticulocytes other immature forms such as normoblasts may appear. White cells gradually increase in number, this increase being due chiefly to the appearance of more polymorphonuclear neutrophils and, later, eosinophils. Platelets likewise become more numerous. The marked anisocytosis decreases and the numerous bizarre red cells eventually disappear. Mean corpuscular volume gradually decreases and usually normal values are found

when the red count has reached 5,000,000 (Fig 29). Hemoglobin frequently does not increase as rapidly as does the number of red cells so that for a time corpuscular hemoglobin concentration values lower than normal may be found. The mean red cell diameter frequently returns within the normal range but, as Price-Jones has stated, completely normal mean diameter and normal variability in size are reached only in a proportion of cases.

That **hemolysis ceases** very readily on liver therapy is shown by the fact that the icterus index falls at about the end of the first week and is within quite normal limits at the end of 3 or 4 weeks. Urobilinogen in the urine begins to decrease in amount at the peak of the reticulocyte response and falls to within normal limits in a few days (Graham *et al.*).

Interesting **metabolic changes** which can only be mentioned here have been observed following liver therapy in pernicious anemia. Riddle has noted a marked increase in the urinary excretion of uric acid beginning within 24 hours of liver treatment. This he attributes to an accelerated rate of development of the red blood cells and a resultant increased destruction of normoblastic tissue. Blotner and Murphy, and Riddle have observed a decrease in the blood sugar during early remission. Blotner and Murphy suggest that liver contains a blood sugar-reducing substance, whereas Riddle feels that the fall of the fasting blood sugar values is related to a metabolic adjustment accompanying early remission. Muller's observations on the blood cholesterol, lecithin-phosphorus and fatty acids have already been alluded to. Alt has observed a striking retention of protein during remission as evidenced by markedly positive nitrogen balances. Basal metabolic rate rose during the increase in the number of reticulocytes.

MAINTENANCE DOSAGE OF LIVER.—Once the blood has returned to normal, the **quantity of liver or liver extract** administered may be reduced. The **maintenance dose** can be determined only by trial and therefore **repeated blood examinations** at intervals of 2 to 4 weeks are necessary until this is established. Subsequent examinations need not be as frequent but it is important to **periodically reexamine** the blood. Since liver therapy is not a cure for pernicious anemia but merely serves to make up for something which is deficient, this form of treatment should be continued indefinitely. In the treatment of the neurological symptoms especially, and with the view of preventing the onset of further degenerative changes in the nervous system, **it is extremely important to maintain the blood at a normal level.** Usually it will be found that at least 300 gm. of liver, or its equivalent, will be needed weekly.

FAILURE OF LIVER TREATMENT.—In the vast majority of instances, liver therapy in pernicious anemia is followed by a rapid remission, the duration of which depends on the continuous use of adequate quantities of liver. Complete or partial failure may result from one of several causes. The presence of **infection or a complicating disease**, such as arteriosclerosis, very frequently prevents complete and satisfactory remission. This fact emphasizes the importance of a careful search for foci of infection in patients suffering from pernicious anemia and the necessity of guarding them against intercurrent infections and complications. When these arise it is well to push the dosage of liver or liver extract which should be given by stomach tube or even per rectum if necessary.

The use of inactive extracts or inadequate doses of potent extracts is another cause of failure. When a reticulocyte response fails to appear in 6 to 10 days in a patient whose red cell count is less than 3 million per cubic millimeter, a careful search should be made for **infections** such as cystitis, pyelitis, cholecystitis and the like and, if these cannot be found, the **potency of the extract** employed may be questioned and another tried. **Whole liver** should be used in addition in all such cases.

Isaacs has pointed out that sometimes "abortive relapses" may occur in pernicious anemia. Loss of appetite and exacerbation of symptoms may occur even though the blood is normal. Such relapses lead frequently to discontinuance of liver therapy with the result that a true hemopoietic relapse follows. Such events should be carefully avoided whenever possible.

Very occasionally patients will be encountered who are entirely refractive to

treatment. In such cases the anemia may have become aplastic in type, and it is well to remember that such bone marrow exhaustion may result from too many transfusions.

Blood transfusion is now seldom necessary in pernicious anemia. **Repeated transfusions** should be avoided since they depress bone marrow activity. In desperately ill patients with red cell counts below 1 million and perhaps in coma, or in those suffering from severe nausea, vomiting and diarrhea, transfusion may serve to tide the patient over until the liver or liver extract given becomes effective. Riddle and Sturgis have shown that **massive doses of liver extract** (30 vials) administered by stomach tube are followed by a reticulocyte response in 48 hours.

In the light of the present inadequate knowledge, we feel that it is advisable to continue the use of **hydrochloric acid** in pernicious anemia. Such treatment may be useful in relieving diarrhea and appears to be of value in reducing the intestinal flora (Hurst, Knott). Porter has suggested that the secretion of hydrochloric acid by the stomach may in some way prevent the onset of neurological changes since in sprue, where gastric acidity is frequent, nerve changes are very unusual. From 4 to 8 c.c. of dilute hydrochloric acid should be given three times a day. This may be given in orangeade or lemonade and should be taken before, during and after the meal.

There appears to be no logical indication for the use of **iron** in uncomplicated pernicious anemia. When chronic blood loss or some other factor which tends to produce the microcytic and hypochromic forms of anemia is associated with the pernicious anemia, however, iron may be found to be of value. Some (Naegeli, Piney) still favor the use of **arsenic** in small doses for its stimulating effect on the bone marrow, but this is rarely needed with liver therapy. Splenectomy is now of only historical interest.

Prognosis—Prior to the introduction of liver therapy the outcome in a case of pernicious anemia was almost invariably fatal. The diagnosis in the very few cases reported as recovered must certainly be held in doubt. Although rarely an acute case progressed rapidly for the worse and died, the majority of patients, after an illness of varying severity, either spontaneously or following the institution of some form of therapy, gradually regained their health. This recovery may have been almost perfect with the disappearance of signs of hemolysis and a rise in the red cell count to 4 million or more. More often it was incomplete and in any event, after an interval of a few months or even years, a relapse followed. Stockton has reported a case in which the remission lasted twenty years. Remissions occurred in 86 per cent of Cabot's large series and 15 per cent of the cases had more than two remissions. Throughout the periods of remission and relapse achylia persisted and the neurologic complaints gradually became worse. Death usually resulted in 1 to 3 years but rarely patients were known to live for as long as 14 years.

The introduction of liver therapy has completely changed the outlook for the patient suffering from pernicious anemia. McKinlay reports that there has been a distinct reduction in mortality from pernicious anemia in England, Wales and Scotland since the introduction of this form of treatment. It appears that as long as adequate dosage is continued the blood can be maintained at normal. The chief dangers to patients at present lie in inadequate dosage, intercurrent infections arising and interfering with the utilization of liver and, finally, complications arising from neurologic disturbances. It is possible that if adequate dosage is maintained the progression of cord degeneration may be prevented. The value of the diagnosis of pernicious anemia before such a time as irreparable changes have taken place in the nervous system, is thus emphasized.

Pathology.—The autopsy findings in Addisonian pernicious anemia disclose certain striking pathologic changes indicative for the most part of the high grade of hemolysis present in this disease, together with the extreme grade of anemia and its long duration. They throw little light upon the actual cause of the disease.

Fatty degeneration is the dominant process in the parenchymatous viscera

and is especially marked in the liver, heart and kidneys. The heart is usually dilated and flabby and contains little or no blood. Its color is a pale yellow.

The red bone marrow is strikingly deepened in color and the yellow marrow of the long bones appears to be transformed into a deep red gelatinous substance often likened to currant jelly. This appearance is usually more striking than that seen in even the severest forms of "secondary" anemia. Histologic examination of the myeloid tissues reveals erythroblastic cells in groups or islands. Megaloblasts are conspicuous. Peabody considers the characteristic histologic change to be hyperplasia of myeloid cells and a decreased tendency to maturation of red cells. Doan found an abnormally large number of clasmato-cytes in the bone marrow in the stage of relapse.

An extraordinary, large deposit of iron in the liver, and to a lesser degree in the spleen and kidneys, attends the continued destruction of red cells. A section of the liver thoroughly treated with a weak solution of ferrocyanide of iron and then washed in a weak aqueous solution of hydrochloric acid assumes a strikingly beautiful blue color.

The mucosa of the tongue is usually atrophied. Inflammatory and atrophic processes in the stomach and intestines are described by some observers (Zadek), but others insist that such changes are only apparent and are due to post-mortem changes (Gulland and Goodall).

In the central nervous system there are disseminated areas of degeneration which are most marked in the posterior and lateral columns.

In two patients who died during a period of liver-induced remission as the result of an intercurrent disease, Zadek could find no histologic changes characteristic of pernicious anemia. Mettier found siderosis greatly lessened during liver-induced remission.

History.—Cases of what would now be called pernicious anemia were recorded by Combe (1823), Andral (1823), Marshall Hall (1837) and others, but it was not until 1855 that the clinical features of the disease were more completely described by Addison, who observed this "idiopathic anemia" in the course of his studies of the suprarenal capsules. Biermer, apparently independently, wrote a more comprehensive account in 1872. In the same year Pepper discovered the changes in the bone marrow, and Ehrlich shortly afterwards described the histologic changes in the blood. Lichtheim called attention to the degeneration in the posterior columns in 1887. William Hunter's researches upon the iron in the liver and other organs (1888) formed the foundation upon which the hemolytic conception of the disease is based. A complete account of the historical aspects of pernicious anemia will be found in the paper by Jamieson.

HEMOLYTIC ANEMIAS

Definition.—The term "hemolytic anemia" embraces a group of anemias of widely varied causation, the unifying characteristic of which is the presence of excessive blood destruction. In some instances hemolysis is the dominant factor and appears to be the cause of the anemia. In other cases the excessive blood destruction, although quite marked, may basically depend on defective blood formation. Pernicious anemia appears to be of the latter type. The hemolytic anemias are distinguished from the nonhemolytic variety of which simple chronic anemia, posthemorrhagic anemia and aplastic anemia are examples. It must be remembered, however, that an etiologic factor which usually produces a nonhemolytic anemia may in some instances be associated with excessive blood destruction.

Pathologic Physiology.—When red cells are destroyed they are taken up by the phagocytic cells of the reticulo-endothelial system where the hemoglobin is converted into bilirubin. This pigment enters the blood stream but, if blood destruction is not too rapid, it is removed by the liver and excreted in the bile. Accumulation of bile pigment in the blood stream, hyperbilirubinemia, occurs when the blood destruction is so greatly accelerated that the liver cannot keep pace. The degree of hyperbilirubinemia may be measured by the icterus index and van den Bergh tests.

In this hemolytic type of jaundice bile does not appear in the urine, hence the name acholuric, but urobilinogen and urobilin are found in excessive quantities and the estimation of these pigments serves as a valuable index of the degree of blood destruction. Excessive quantities of these pigments are also found in the duodenal contents and feces. Their origin has already been discussed.

It is very rare for actual solution of the red cells to take place in the blood stream with the liberation of hemoglobin (hemoglobinemia). Such an event occurs only when large numbers of red cells (about 1/60 of the total number) are abruptly destroyed. In such instances the urine appears red although no red cells can be found (hemoglobinuria).

Symptomatology.—Hemolytic anemias may be acute or chronic, febrile or afebrile and show the widest divergence in etiology, gravity and general symptomatology. The skin and sclerae of such patients appear yellowish as the result of the hyperbilirubinemia, and may even show marked jaundice. The spleen is frequently enlarged, but again this feature varies with the severity of the condition and the nature of the causative factor. The blood usually shows marked variation in the size and shape of the red corpuscles with numerous microcytes and fragments of red cells. Not infrequently there is evidence of bone marrow stimulation. Normoblasts and microblasts usually constitute a majority of any erythroblasts present. Later aplasia may follow with reduction not only in the number of red corpuscles but of white cells and platelets as well. Increased fragility of the red cells to various strengths of salt solution is characteristic of the purer forms.

Acute hemolytic anemia may result from:

(1) *Sepsis*.—An anemia of profoundly hemolytic type may develop with extraordinary rapidity so that in a few days the red blood count may have dropped below 1 million cells per cubic millimeter. Such anemias have been described most frequently in association with sepsis following childbirth or abortion, but scarlet fever, pneumonia and malignant endocarditis have also given rise to the same condition. Macintosh and Cleland in 1902 and later Lederer, Moschowitz and Brill described an "acute febrile anemia" of sudden onset, irregular fever, leukocytosis, hyaline thrombosis of the terminal arterioles and capillaries, and of unknown etiology. Brill found treatment with small and frequently repeated blood transfusions successful.

(2) *Poisons*.—Benzene compounds such as benzene itself (benzol), phenol, toluol, nitrobenzene, trinitrotoluol, phenylhydrazine, pyrodine, toluodiamine, aniline and its derivatives acetanilid and phenacetin, potassium chlorate, the nitrites and metals such as lead may all produce an acute hemolytic anemia. The same substances may also produce chronic hemolytic anemia or even aplastic anemia.

Acetanilid, which is the chief constituent of many headache powders, as well as other coal tar products, leads to the formation of methemoglobin which is useless for respiratory purposes. The blood becomes a dark chocolate color and cyanosis may become marked. Anemia is usually slight but an acute hemolytic anemia may result. Extreme anisocytosis, numerous fragmented cells and normoblasts, leukocytosis and a greatly increased number of platelets are frequently observed.

Kegel, McNally and Pope have recently shown that an anemia in which bilirubinemia and leukocytosis are noteworthy may be caused by methyl chloride poisoning from domestic refrigerators.

(3) Blood destruction so excessive and so abrupt that *hemoglobinuria* results, occurs following the transfusion of incompatible blood, in the condition known as paroxysmal hemoglobinuria, in blackwater fever, more rarely in other human infections, and occasionally after extensive burns, snake venom poisoning and in poisoning by the drugs mentioned in the preceding paragraphs.

Certain anemias of the acute hemolytic type here described were termed *leukanemia* by Leube and Arneth because of the presence of many young marrow leukocytes and the erroneous belief that they represented a cross between anemia and acute leukemia.

Chronic Hemolytic Anemia.—The purest type of chronic hemolytic anemia occurs in the disease known as HEMOLYTIC JAUNDICE. In this condition, which is fully described elsewhere, there is a constant increased destruction of red cells with hyperbilirubinemia and splenomegaly. Bile pigments are not found in the urine but urobilinogen and urobilin are present. The anemia depends on the balance between the destruction and the formation of red cells and frequently varies with the hemolytic crises so characteristic of this disease. There is evidence of stimulated bone marrow activity as manifested by reticulocytosis, which is often as high as 20 per cent and may even be 50 per cent, as well as by the presence of normoblasts and microblasts, and increased numbers of white cells and platelets. The red cells are usually smaller than normal. The finding of macrocytes is unusual. Increased fragility of the red cells to various strengths of salt solution is a characteristic feature.

Ill defined cases of chronic hemolytic anemia may occasionally be encountered in which diagnosis is difficult. Minot discusses these at some length. There may be instances in which hyperbilirubinemia and an icteric tint of the skin and sclerae are found in the absence of anemia or characteristic signs of hemolytic jaundice. There may be acholuric jaundice with polycythemia and splenomegaly. Minot points out that occasionally in diseases which are usually associated with a simple chronic anemia, there may be evidence of increased blood destruction.

The hemolytic type of anemia which sometimes is observed in pregnancy, fish tapeworm infestation, cancer and syphilis remains to be considered.

HEMOLYTIC ANEMIA ("PERNICIOUS ANEMIA") OF PREGNANCY.—In addition to the simple, so-called "physiologic" anemia frequently observed in pregnancy, a severe, hemolytic anemia is occasionally encountered in the latter half of the period of gestation or in the puerperium (Larrabee, Smith, Hoskin and Ceiriog-Cadle). This is a form of anemia which is distinct from pernicious anemia although it may closely resemble the latter. There may be sore mouth, vomiting and diarrhea, while weakness, dyspnea, palpitation, pallor and edema of the feet and legs are common. Evening fever without any evidence of infection and with negative blood cultures, has been described (Aubertin). The spleen may be palpable, and there is frequently evidence of excessive bone marrow activity. Although not unusually leukocytosis and an increased number of platelets are found, these may be reduced in numbers, anisocytosis and poikilocytosis may be marked, and megalocytes and even megaloblasts have been reported. As a rule, however, macrocytosis is less marked than in pernicious anemia. Achlorhydria may or may not be present. The absence of nervous symptoms and the fact that hemolytic anemia of pregnancy more frequently occurs under 35 years of age, aid the differentiation of this condition from true pernicious anemia.

The etiology of the hemolytic anemia of pregnancy is unknown. Constitutional abnormality (Esch), excessive demands on a bone marrow which has been too greatly taxed either by earlier pregnancies or by previous ill health (Alder) and the activity of toxins produced in the placenta (Aubertin, Schneider) have been suggested as causative factors. Some of the cases reported have no doubt been confused with acute hemolytic anemia resulting from puerperal sepsis.

These cases go on to either permanent recovery or death, usually rather rapidly and without remission or relapse. The mortality has been given as 50 to 75 per cent. If recovery takes place there appears to be little tendency to recurrence in succeeding pregnancies, although such cases have been reported (Murdock). It is doubtful whether termination of the pregnancy has any beneficial effect on the anemia. Frequently repeated transfusions seem to be of benefit (Larrabee), and recently very favorable results have been reported following the use of liver and liver extracts (Brault, Peterson *et al.*).

TAPEWORM ANEMIA.—An anemia practically identical with pernicious anemia may sometimes be associated with infestation with the fish tapeworm *Bothriocephalus latus* (*Diphylobothrium latum*). Such infestation occurs in the Scandinavian countries and has been reported in Minnesota, Michigan and Manitoba (Canada). Bilirubinemia, an identical blood picture, and even achlorhydria and nervous symptoms have been described although the last two features

have not been noted in all cases. Recovery is said to follow expulsion of the worm.

Several observations suggest that the presence of the worm is not in itself sufficient to cause the production of this macrocytic, hemolytic type of anemia but that possibly a constitutionally susceptible host or other predisposing factor is necessary. Ehrström estimated that in Finland only from 0.1 to 0.5 per cent of those infected with the tapeworm develop anemia. Piney states that "it is fairly common for several members of the same family to suffer from the disease, although servants and others in the same household are free from it, in spite of being infested with the parasite." Piney furthermore mentions that Schaumann has been able to observe and record cases in which cure following expulsion of the worm was followed many years later by the occurrence of relapses of "typical 'pernicious' character not accompanied by any infestation." Again, Barron and Isaacs, Sturgis and Smith found that the presence of the worm did not alter the beneficial effect of liver therapy on the anemia. According to Barron, the removal of the tapeworm apparently does not alter the course of the anemia.

It is most unusual for a hemolytic type of anemia to be associated with the presence of other types of parasites. Naegeli has observed two cases associated with *Taenia saginata* infestation and Bardenwerper reported a case in a child associated with the presence of *Ascaris lumbricoides*.

HEMOLYTIC ANEMIA IN CANCER.—Very rarely the blood picture in cases of cancer, particularly that involving the gastro-intestinal tract, closely resembles that of pernicious anemia. Usually careful scrutiny reveals the fact that some of the characteristic features of pernicious anemia are absent. In those instances in which pernicious anemia cannot be distinguished, the association of two different diseases may well be considered. Means has recently described a case of pernicious anemia in which carcinoma of the stomach developed following complete remission of the anemia after the use of liver diet.

SYPHILIS, particularly the tertiary congenital type, may be associated with a very severe anemia. The blood picture is usually that of simple chronic anemia but several instances of a "pernicious type" of anemia have been described. In view of the frequency of syphilis and the extreme rarity of macrocytic hemolytic anemia in association with this disease, however, the accidental association of two distinct and unassociated diseases must certainly be considered in explanation of such findings. Cummer found no final proof that syphilis may produce an anemia of "pernicious" type.

SICKLE CELL ANEMIA

Definition.—This is a hemolytic anemia, hereditary and familial in nature and apparently peculiar to the Ethiopian race, which is characterized clinically by pallor and a greenish-yellow discoloration of the sclerae, symptoms of anemia, abdominal pain, rheumatoid manifestations and leg ulcers, and morphologically by the presence or formation of peculiar sickle- and oat-shaped red corpuscles in the blood, as well as by evidence of excessive blood destruction and active blood formation.

Etiology.—The etiology of sickle cell anemia is unknown. The disease appears to be confined to members of the negro race or individuals whose blood contains an admixture of negro blood. The few reports which purport to contradict this statement are unconvincing. Stewart's patient, an apparently white child of Cuban descent whose family could be traced with certainty for the last three generations, possessed facial characteristics which, according to Stewart, suggested a mixture of negro with white blood. Cooley and Lee report the finding of sickle cell anemia in two brothers of a Greek family, and Lawrence found "sickle-shaped, sausage-shaped and filamentous red cells" in the blood of a white woman of Scotch-Irish-Spanish descent who was suffering from a mild anemia, as well as in the blood of her brother, sister and niece. He also found such cells in the blood of three healthy white students. Although nothing is known concerning the significance of elliptical and sausage-shaped red corpuscles such as were originally described by Dresbach and appeared to have

been present in the blood of Lawrence's patients, there are certain important distinctions between these cells and the abnormal erythrocytes found in the blood of negro patients suffering from sickle cell anemia. The most important of these is the fact that no time element is needed to elicit the formation of elliptical red corpuscles, whereas in the blood of certain negroes, sickle-shaped, filamentous and, what is still more characteristic, oat-shaped red corpuscles are formed when their blood is allowed to stand in a sealed fresh preparation. Neither in the blood preparations of Lawrence's patients nor in those of Cooley and Lee were oat-shaped corpuscles reported.

Sickle cell anemia was first described by Herrick in 1910. Sydenstricker in 1924 pointed out that the blood of many negroes in good health shows the sickle cell phenomenon. He spoke of this as the "latent phase." Cooley and Lee found the sickle cell trait in 7.5 per cent of 400 negro dispensary patients, and Brandin records an incidence of 6.7 per cent among negro industrial workers. Only a small proportion of these individuals developed anemia. The sickle cell trait is hereditary and is transmitted according to the Mendelian law of heredity. Sydenstricker found 80 cases in 10 family groups.

The sickle cell phenomenon seems to be a property of the red cells (Huck) rather than of the plasma or a substance contained therein as Joseph's experiments seemed to show. Hahn and Gillespie have shown that the crescentic shape is assumed by the red corpuscles of an affected individual when they are suspended in an atmosphere without oxygen. Furthermore, they have found that the distortion occurs slowly or not at all in alkaline suspensions, whereas acidity favors its production. Exposure to oxygen or carbon monoxide is effective in restoring sickle cells to a circular form. Again, cells fixed in solutions which are capable of acting as oxidizing agents, such as Zenker's solution, assume the circular form, whereas ferrous ammonium sulphate solution and formaldehyde gas effectively fix sickle cells in their characteristic form. Scriver and Waugh have been able to produce similar variations in the number of sickle cells in the blood *in vivo* by changing the partial oxygen pressure. These experiments suggest that "the crescentic shape is stable when the contained hemoglobin is in the reduced state and the circular shape is stable when the hemoglobin is combined."

The factors which precipitate the sickle cell distortion in the living subject are unknown. The experiments of Hahn and Gillespie suggest that anoxemia is an important factor. Graham suggests that toxic, metabolic or infectious agents are the exciting factors in hereditarily predisposed individuals. Certainly attacks not infrequently follow exposure to cold or infection or are associated with the presence of some other disease such as tuberculosis. Such factors may cause the formation of sickle cells in the blood and these, according to Hahn and Gillespie, are more susceptible to hemolytic influences than are normal red corpuscles.

Symptomatology.—Individuals suffering from sickle cell anemia frequently give a history of recurrent attacks of weakness, ready fatigability or other symptoms of anemia; or "rheumatism" with aching pains in the joints or muscles; or, not uncommonly, attacks of abdominal pain and jaundice. Members of the family may have suffered from or died following the onset of similar symptoms. The complaints which may cause the patient to present himself are quite varied and not infrequently may suggest the presence of some infection or disease of the abdominal organs. At times there is vomiting and sharp, stabbing pain in the epigastrium or left hypochondrium. This pain may be so severe that together with the associated prostration and abdominal tension, the diagnosis of one of the abdominal emergencies at once suggests itself. These attacks of abdominal pain may be associated with periods of excessive blood destruction or may be the result of splenic infarction or perisplenitis. Leg ulcers, particularly near the ankles, are common. They may arise as the result of very slight trauma and may last a long time, perhaps partly as the result of the improper care with which they are often treated by the patients.

Affected individuals not unusually are ill-nourished and may show marked retardation of physical development. There may be a low-grade fever, or the

temperature may be quite high (103° F.) and the patient appear acutely ill. The pallor of the patients is readily noted on examination of the mucous membranes or the palms of the hands. The sclerae are greenish-yellow in color. There is frequently general glandular enlargement, but Sydenstricker found splenomegaly in only 11 of 71 cases. There may be any of the signs common to anemia, such as systolic cardiac murmurs. The liver may be just palpable. An ulcer or scar may be found on the leg, usually above the ankle. Interesting case reports are presented by Smith and by Fradkin and Schwartz as well as by the writers already mentioned.

LABORATORY FINDINGS.—Anemia may be quite marked, the red cell count ranging during the stages of anemia from 4 to 1 million. Hemoglobin and volume of packed red cells may or may not be proportionately reduced so that normal or high values for corpuscular volume and corpuscular hemoglobin (or volume and color index) may be found. Leukocytosis is present and frequently marked (10,000 to 30,000 or more per c.mm.) in acute cases and platelets are also increased in number (300,000 to 500,000 per c.mm.). A few sickle or rod-shaped cells may be made out on examination of the blood smear, which otherwise reveals such evidence of over-active blood formation as marked variation in the size of the red cells, polychromatophilia and numerous nucleated red corpuscles. The latter consist chiefly of normoblasts, although macroblasts are also found. Sydenstricker noted nucleated sickle cells in 3 of 80 cases. Occasionally punctate basophilia (stippling) is noted. Reticulocytes are commonly increased (15 to 25 per cent). Scriver and Waugh point out that the majority of the reticulocytes are circular in form, an observation which suggests that sickling is a property of the more mature forms of red corpuscles.

We have been struck by the large size of some of the red corpuscles in 3 cases of sickle cell anemia observed by us. One hundred cells measured in each of these cases showed diameters ranging from 6 to 13.5 μ . The sickle cells were, on the average, 15 μ in length and 2.5 μ in width.

The leukocytes of the granular series may show a "shift to the left," that is, an increase in the number of younger forms, and even myelocytes may be encountered. Eosinophilia is not infrequent. The monocytes may be increased in number. Huck described red corpuscles engulfed by cells of the large mononuclear variety.

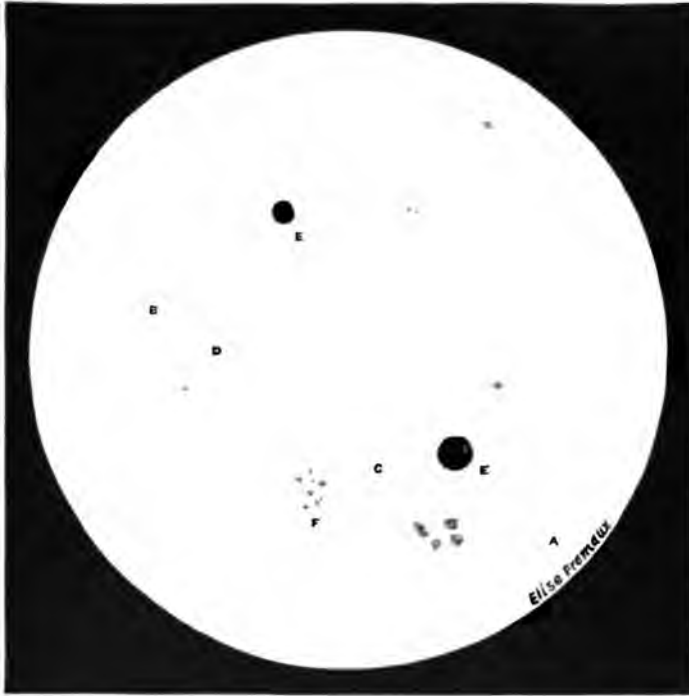
Although frequently a few sickle cells are noted in the examination of the blood smear, it is necessary to deprive the blood corpuscles of oxygen in order to elicit the sickle cell phenomenon. This may be done by placing a fresh drop of blood on a thin cover-slip, inverting this on a slide and sealing the preparation by means of petrolatum or Canada balsam. It is very essential that clean glassware be used. The drop of blood should be just large enough to make a thin film. If blood so obtained is kept at room temperature the sickling phenomenon will occur in 2 to 24 hours in the blood of all individuals who possess the "sickle cell trait." The red corpuscles will be seen to assume various bizarre patterns, the chief of which are sickle, oat and stellate in shape. Fine drawn-out processes frequently extend from these cells. Similar changes may be observed in blood from patients who present the sickle cell phenomenon that has been left in a counting chamber for an hour or more, or in oxalated blood that has been kept tightly corked at room temperature for 24 hours.

Bleeding time and coagulation time are normal. Blood of affected individuals has usually shown normal or increased resistance to hypotonic salt solutions. During the stage of blood destruction there is *hyperbilirubinemia*, as indicated by a high icterus index and a positive indirect result by the van den Bergh test.

The *urine* examination may reveal low fixed specific gravity, albumin, hyaline casts and perhaps diminished phenolsulphonephthalein excretion. Urobilinogen and urobilin are greatly increased during the stage of hemolysis. Gas-tric analysis reveals no characteristic abnormality.

Diagnosis.—It is evident from the variety of symptoms that may be encountered in sickle cell anemia that a mistake in diagnosis may very readily be made. Particularly confusing are the symptoms relating to the abdomen. These

C. P. VII—Musser & Wintrobe.



SICKLE CELL ANEMIA (WRIGHT'S STAIN). $\times 950$.

a, Normocyte; *b*, macrocyte; *c*, sickle-shaped, red corpuscle; *d*, polychromatophilic red corpuscle; *e*, normoblasts; *f*, punctate basophilia.

are common and may suggest the presence of an abdominal emergency. In any doubtful case a fresh drop of blood should be examined in the manner already described. Such a precaution may serve to rule out gall-bladder disease, peptic ulcer, appendicitis, intestinal obstruction, typhoid fever, tuberculosis, syphilis and chronic osteomyelitis, for all of which conditions we have known sickle cell anemia to be mistaken.

It may be emphasized, however, that any of these conditions may be associated with sickle cell anemia and may, perhaps, have precipitated the anemia. Gall-bladder disease and especially tuberculosis have been observed in a number of individuals suffering from sickle cell anemia.

The *elliptical red corpuscles*, first described by Dresbach and discussed in papers by Bishop, Huck and Bigelow, Lawrence, Hunter and Adams, and Günther, should not be confused with sickle cells. Elliptical cells are found in the blood of both the Caucasian and Ethiopian races. They show blunt ends rather than the pointed ends characteristic of the abnormal cells found in sickle cell anemia and no time element is required to elicit them. Anemia may be absent even when 80 per cent of the corpuscles are elliptical or oval in form.

Familial hemolytic jaundice is differentiated by the fact that sickle cells are absent and splenomegaly and decreased resistance of the erythrocytes to hypotonic salt solution are present.

In pernicious anemia, achlorhydria, tongue and neurologic symptoms, leukopenia, usually more marked macrocytosis, and the absence of sickling are differentiating features.

Treatment.—No form of treatment employed has so far affected the sickling phenomenon in any way. Aside from general symptomatic treatment, the only measures which appear to have been of value are frequently repeated **transfusions** and **splenectomy**. The latter, suggested by Sydenstricker, was first carried out by Hahn and Gillespie, and since then has been performed by Stewart, Landon and Lyman and others. This method of treatment is still in the experimental stage. Improvement has been noted, particularly in those instances in which splenomegaly was present. Liver therapy has had no noteworthy effect.

Prognosis.—The sickle cell trait in itself is compatible with perfect health and long life (Hahn). Those suffering from sickle cell anemia usually pass through a series of remissions and relapses. They are prone to infections, one of which may be fatal. Attacks of anemia are more frequent in childhood and become less frequent as the patient becomes older, so that in adults the prognosis as to health and life is much better than in children.

Pathology.—At autopsy the usual evidence of anemia and excessive blood destruction in the form of fatty degeneration and hemosiderosis are found. The bone marrow is hyperplastic. Sydenstricker, Mulherin and Houseal reported the finding of sickle-shaped and filiform erythrocytes in bone marrow at autopsy and we have observed similar long filamentous bands of erythrocytic material in the bone marrow removed during life. The spleen is often small as the result of atrophy of the pulp tissue. Healed infarcts have been noted. Rich found characteristic malformation of the splenic sinuses immediately about the malpighian follicles with collections of pools of blood in fibrosed and atrophic areas.

THE ANEMIAS OF CHILDHOOD

Difficulties are encountered in the diagnosis of anemias in childhood not only because of the frequently greater difficulty in discovering a cause, but also because of the difference in the response of the hematopoietic system of children, particularly infants, as compared with that of adults. The difference is largely a variation in the degree of response rather than in its nature. In infants reversal to a fetal form of hematopoietic activity more readily occurs, and for any given stimulus, as compared with the reaction of an adult, young erythroblasts and perhaps megaloblasts will appear rather than normoblasts and reticulocytes, myelocytes and myeloblasts will be encountered instead of late myelocytes and unsegmented neutrophils, and the spleen, lymphatic glands and

liver will more frequently become enlarged. Perhaps, also, bone marrow exhaustion may more readily take place.

The anemias of childhood have been very inadequately studied. Because of the difference in response and an attempt to study the blood of the infant on the basis of conceptions derived as the result of the study of adults, numerous cases have been reported as new or unusual clinical entities which really represent a qualitative and often also a quantitative variation in the response of an incompletely developed human organism to commonly encountered etiologic factors. Bacterial infection, syphilis, tuberculosis, nutritional and gastro-intestinal disturbances are very frequently associated with anemia in childhood, an anemia which may become quite severe. Blackfan, Baty and Diamond describe an anemia of prematurity and an anemia of the newly-born. Hemolytic jaundice, sickle cell anemia, leukemia and, very, very rarely, pernicious anemia may occur in childhood. Hemorrhage may be followed by an unusual response. In 1890 Rudolf von Jaksch described an anemia of infants characterized by deficiency in hemoglobin and erythrocytes, marked anisocytosis and poikilocytosis, numerous erythroblasts and macroblasts, extreme leukocytosis with relative lymphocytosis, splenomegaly and enlargement of the liver and lymphatic glands. To this condition he gave the name *anemia pseudoleukemica infantum*.

The patients described by von Jaksch were all under 3 years of age and usually 3 to 6 months old. The onset of their illness was insidious and the complaints included enlargement of the abdomen, listlessness, ready fatigability and weakness, gastro-intestinal disturbances, marked pallor and often irregular fever. Not infrequently there was evidence of excessive blood destruction. A majority of the patients recovered completely.

There is now little doubt that the syndrome described by von Jaksch is not a disease entity but represents a symptom complex which may be associated with a large variety of factors, among which may be mentioned rickets, malnutrition, gastro-intestinal disturbance, syphilis, tuberculosis and a number of other infections. For the adequate treatment of such an anemia it is obviously essential to discover and alleviate the underlying cause. In addition, symptomatic and hygienic measures are indicated. Iron and arsenic may be of value and transfusions are indicated when the anemia is severe. Josephs finds that copper is of some value in the treatment of the nutritional anemias and in accelerating the effect of iron in the anemia resulting from infection. Splenectomy has sometimes been employed in cases of obscure etiology with results that have not been strikingly beneficial.

Cooley in 1925 described a condition which he termed *erythroblastic anemia* or *erythroblastemia*. This condition is characterized by chronic progressive anemia, the most striking feature of which is the presence of excessive numbers of nucleated red corpuscles in the peripheral blood. Leukocytosis is quite marked (10,000 to 30,000) and there is evidence of excessive blood formation and destruction. A characteristic facies is described: prominent eyes, puffy eyelids, frequently an epicanthal fold, high forehead with prominent frontal bosses, and a skin of muddy yellow color. The symptoms are those of anemia and abdominal tumor. The liver, spleen and lymph glands are enlarged. Unusually prominent medullary trabeculations and thin bone cortex are characteristic roentgenologic findings. Cooley observed this disease in children of Greek, Italian and Syrian parentage. From the cases cited by Blackfan and his associates a familial tendency may be suspected. The prognosis in this type of anemia is as yet undetermined and the treatment is symptomatic.

It is obvious that differentiation of anemias as they appear in childhood can be made only by a very thorough study of the individual cases. In the study of the blood, accurate red cell, white cell and platelet counts and hemoglobin determinations, painstaking morphologic studies, including reticulocyte counts and determinations of the size of the red corpuscles, estimation of the degree of blood destruction, determination of the resistance of the corpuscles to hypotonic salt solution and a test of the blood for the sickle cell phenomenon may be required. Cooley's observations suggest, furthermore, that roentgenologic studies of the bones may be of value.



ERYTHROBLASTIC (VON JAKSCH'S) ANEMIA (WRIGHT'S STAIN). $\times 950$.

a, Normoblasts; *b*, microblasts; *c*, normoblast showing karyorrhexis; *d*, young normoblast showing punctate basophilia; *e*, lymphocyte.

POLYCYTHEMIA

The term polycythemia signifies an increase above the normal count in the number of red blood corpuscles. It must be borne in mind in this connection that 5 million cells per c.mm. represents the lower limit of normal in males and that the normal variation in number of red corpuscles is 5 to 6.5 million in men and about 4.4 to 5.3 million in women (Wintrobe).

Polycythemia may be transient or permanent, trivial or grave, relative or absolute. *Relative polycythemia* is a temporary, transient condition in which the number of red corpuscles per cubic millimeter is increased, although the total number of red cells in the body is normal. The relative increase in the number of cells is due to a decrease in the plasma volume such as results from loss of fluid by excessive perspiration and lung ventilation (violent exercise), severe vomiting, profuse diarrhea and the like.

Transient polycythemia may be the result of vasomotor and psychic influences. Ferrari pointed out that emotional excitement may cause a sudden increase in the red cell count amounting to 0.5 million cells or more per c.mm. Izquierdo and Cannon have shown that this rise is the result of liberation of adrenaline and consequent contraction of the spleen.

By *absolute polycythemia* is meant an increase in the number of red corpuscles per cubic millimeter which is associated with an increase in the total number of cells in the blood. Such an increase is not necessarily associated with an augmentation in the total blood volume, although this frequently occurs as well.

Two forms of absolute polycythemia are distinguished, namely, erythrocytosis and erythremia. These terms are employed with the same significance as the terms leukocytosis and leukemia. *Erythrocytosis* denotes an increase in the number of red corpuscles in response to some known stimulus, whereas the designation *erythremia* is reserved for a disease of unknown etiology.

ERYTHROCYTOSIS

Erythrocytosis represents an effort to compensate for oxygen want. As Fitz has stated, oxygen want may arise in one of three ways:

(1) *Defective saturation of arterial blood with oxygen.*—This may result from diminished atmospheric pressure or impaired pulmonary ventilation.

In association with the ascent of high altitudes there occurs in the blood of healthy individuals an increase in the number of red corpuscles and the quantity of hemoglobin. This rise is immediate and is probably the result of a redistribution of corpuscles rather than an actual augmentation in their total number, and depends on the liberation of red cells stored in the spleen. Residence at high altitudes is followed after several days by an increased formation of cells, a true erythrocytosis.

Chronic pulmonary disease such as chronic bronchitis and emphysema, and stenosis of the air passages gives rise to erythrocytosis in individuals whose health is otherwise good.

(2) *Slowing of the circulatory rate of the blood* permits an excessive proportion of oxygen to be used up in the capillaries and therefore results in oxygen want in the tissues. This occurs in many forms of chronic heart disease. When mitral stenosis is associated with long continued chronic passive congestion of the lungs, erythrocytosis arises. In congenital heart disease, particularly when there is pulmonary stenosis, counts of 7 to 8 million or more red cells per c.mm. are commonly observed. In two cases examined by us the white corpuscles were not increased in number or abnormal in form, an important point of distinction between this condition and erythremia.

(3) *Defect in the hemoglobin of the blood* may give rise to erythrocytosis. Such a condition has been observed in poisoning by various chemical and bacterial agents such as adrenaline, digitalis, arsenic, caffeine, nicotine, benzol derivatives, phosphorus, thorium X, radium and opium (Lamson). The formation of hemoglobin compounds which are useless for respiratory purposes, as occurs

in carbon monoxide poisoning or when methemoglobin is formed as the result of excessive use of coal tar derivatives, may be followed by a marked increase in the number of red corpuscles.

ERYTHREMIA

Synonyms.—Polycythemia vera, polycythemia rubra, splenomegalic polycythemia, myelopathic polycythemia, Vaquez' disease, Osler's disease.

Definition.—Erythremia is a slowly and intermittently progressive, ultimately fatal disease of unknown etiology characterized by a striking and often excessive increase in the number of erythrocytes and in the total blood volume, and clinically by a peculiar red cyanosis, splenic enlargement and symptoms associated with the greatly increased blood volume.

Etiology.—This is a disease of late middle life. No known predisposing factors have been described with the exception that a familial occurrence has been noted in some instances; Engelking described 5 cases in one family in 3 generations.

Minot and Buckman, Harrop, and Parkes-Weber and Bode, among others, have discussed the etiology of erythremia in some detail. A condition such as is found in erythremia might conceivably arise from (1) a prolongation of the life of the red corpuscles; (2) diminished destruction, or (3) increased formation. The first of these possibilities has not been shown to exist, while blood destruction appears to be normal or even in excess of normal in this disease. Increased blood formation is suggested by the marked hyperplasia of erythropoietic and leukopoietic tissues and by the excessive number of reticulocytes, the not infrequent finding of polychromatophilia and normoblasts, and the presence of increased numbers of leukocytes and platelets.

The resemblance of erythremia and leukemia has been frequently commented upon. The blood picture of the former not unusually suggests that a "leukemic" process is associated and every combination of the two conditions has been described: frank combination of erythremia and leukemia (Blumenthal); a change from erythremia to anemia and leukemia (Hirschfield, Herzheimer, Minot and Buckman, Detre, Makarevitch) and *vice versa* (Winter); and marked eosinophilia with erythremia (Di Guglielmo, Hay and Evans).

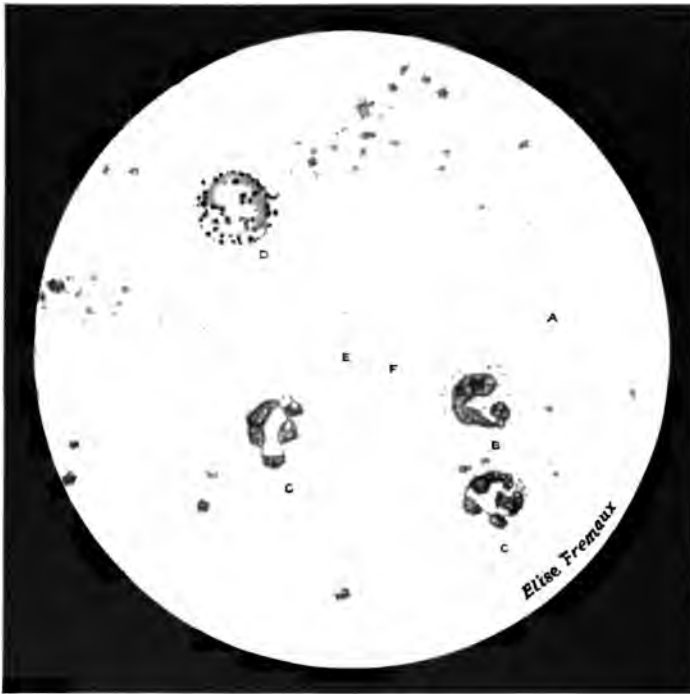
Minot and Buckman consider erythremia to be primarily a disease of red marrow analogous to leukemia and suggest that this disease may represent a type of malignant tumor. It may well be asked, as Hay and Evans do, what is the ultimate stimulus to such a neoplastic growth. Harrop points out that in erythremia there is bone marrow hyperplasia and proliferation of normal elements in contrast to the greatly disordered activity with megaloblast proliferation which occurs during a relapse in pernicious anemia. The cellular hyperplasia shows no diminished tendency toward the differentiation of mature erythrocytic cells. He suggests that "the condition of the bone marrow may be regarded as secondary to one or several different factors causing overstimulation." The lack of striking differences between erythrocytosis and erythremia is cited, and such constitutional factors as structural changes in the lungs which may impede normal oxygen diffusion, variation in the susceptibility of individuals to the stimulative action of impaired circulation, as well as the occurrence of hormonal imbalance in erythremia, are mentioned for consideration.

Symptomatology.—The disease is insidious in its development and its victims may be wholly unconscious of its presence until their attention is called or attracted to the peculiar red cyanosis of the skin and mucous membranes, so marked and characteristic of the established disease. The patient usually consults the physician because of failing reserve, lassitude or even a somewhat rapidly developed state of actual exhaustion.

The excessive blood volume may cause dyspnea, palpitation or a sense of cardiac oppression. There may be weakness or easy fatigability. Edema of the lower extremities may develop. Gastro-intestinal symptoms are inconstant and variable in character and degree. Constipation is relatively common; anorexia may be recurrent or persistent, and cases associated with vomiting seizures are encountered. The last may be wholly unassociated with the ingestion of

C. P. IX—Musser & Wintrobe, Figs. A and B.

PLATE IX



ERYTHREMIA. (Wright's stain, $\times 950$.) (a) myelocyte; (b) juvenile neutrophil; (c) segmented neutrophils; (d) basophil; (e) and (f) basophilic erythrocytes, punctate and diffuse.

food. Epigastric oppression and flatulence are relatively common occurrences and severe abdominal pain may occur.

Hemorrhage from the nose, gums, stomach, bowels and uterus may take place. Cutaneous purpuric manifestations are unusual. Joint disturbances of some severity and cramp-like pains, especially over the bones, are not uncommon. The frequency of nervous symptoms has been emphasized by Christian and by Brockbank. Headache is common. Vertigo may be so severe as to completely invalidate the patient. Irritability, insomnia, lack of power of concentration and other mental symptoms are frequently encountered. Tinnitus, blurring of vision, various paresthesias, staggering gait, thickness of speech, muscular twitching and even paralysis have been described. It is worthy of note, however, that objective neurologic changes occur only in association with vascular accidents such as hemorrhage and thrombosis. Brown and Giffin have recently pointed out that peripheral arterial disease is relatively common in erythremia and may cause unusual symptoms, many of which are relieved by reduction in blood volume and viscosity.

The appearance of the patient is usually quite striking. The face and ears exhibit a peculiar dusky redness seen in no other disease. This color is quite distinct from ordinary cyanosis, however intensive, in that the red dominates the color field as far as the face is concerned. The extremities are markedly cyanotic. The depth and degree of the cyanosis is greatly intensified by exposure to cold and the dependent position. It has been pointed out that in some instances the characteristic color may be absent and even pallor may occur as the result of vasoconstriction or peripheral circulatory failure. Even in these cases, however, the extremities tend to remain colored.

Enlargement of the spleen is present in at least 75 per cent of cases and may attain large proportions. The spleen is smooth and indurated. Enlargement of the liver occurred in 57 per cent of Brown and Giffin's cases.

The blood pressure is frequently normal or only slightly elevated. In 44 of the 66 cases reported by Lucas the systolic pressure was less than 170 mm. Geisböck has described a syndrome which he feels deserves special recognition and which he has designated "polycythemia hypertonica." Together with polycythemia, there is high blood pressure but no splenic enlargement. Parkes-Weber does not consider such cases to be examples of erythremia but rather instances of renal and vascular disease.

Gans has described firm, red, tender nodules in the thoracic and abdominal skin of patients suffering from erythremia. These nodules consist of perivascular collections of oxydase-positive cells.

LABORATORY FINDINGS.—The number of red corpuscles per cubic millimeter is usually greatly increased, values ranging between 8 and 12 million per c.mm. being quite usual. Higher and lower values have been recorded. The hemoglobin usually is not proportionately high. The values range between 18 and 24 gm. per 100 c.c. of blood. Packed red corpuscles form 55 to 70 per cent of the blood as a rule. Leukocytosis is usual (15,000 to 30,000 per c.mm. or more) and the platelets are commonly increased in number. The blood is dark red, thick and sticky, its viscosity being frequently 5 to 8 times the normal. Sedimentation rate is extremely slow. The blood plasma usually is normal in color, thus indicating that blood destruction is not excessive, although occasionally slight hyperbilirubinemia may be observed. Bleeding time is normal and coagulation time may be slightly accelerated. Minot and Buckman noted a lengthening in the range of resistance to hypotonic salt solution.

The red corpuscles may be normal in size or somewhat smaller than normal. Anisocytosis and poikilocytosis may be absent or quite marked. Polychromatophilic red corpuscles may be noted but nucleated red corpuscles are not very common. Reticulocytes are frequently increased in number. Granulocytes compose the greater proportion of the white cells and immature forms are not infrequently observed.

The total blood volume is greatly increased and may be more than twice normal. Rowntree, Brown and Roth found in 50 cases total blood volumes of 121 to 246 c.c. per kg. of body weight as compared with the normal mean volume of

87 c.c. Plasma volume in these cases was increased little or not at all (45 to 88 c.c. per kg. of body weight as compared with the normal mean of 51 c.c.).

Albumin and hyaline and granular casts are not unusually found in the urine. The basal metabolic rate is frequently increased. Isaacs has suggested that this is related to increased destruction of the nuclear material of the blood elements.

Diagnosis.—Erythremia must not be confused with erythrocytosis. The causes of the latter condition have already been discussed. A thorough search should be made for one of these. Splenomegaly is rarely associated with erythrocytosis and in the latter increase of total blood volume is absent or usually not marked. Finally, leukocytosis is usually not associated with erythrocytosis and abnormal red and white blood elements are absent.

Patients suffering from erythremia may first present themselves because they have recently suffered from a large hemorrhage. In such cases the red cell count and hemoglobin may be reduced to normal values or lower, whereas the leukocytosis so commonly encountered in erythremia often becomes even more pronounced. This leukocytosis together with the myelocytes and other young forms of granulocytes, and the splenomegaly, may lead to the erroneous diagnosis of myeloid leukemia. The possibility of the occurrence of such an episode in the course of erythremia should be borne in mind.

Treatment.—Treatment of erythremia is wholly **symptomatic**. The greatest stress should be laid on the adoption of a **mode of life** which will conserve the patient's slowly waning strength and a diet that will fill his nutritional needs without involving gastro-intestinal disturbances.

The **repeated withdrawal of blood** is of temporary value. **Irradiation** of the long bones has recently been favorably reported by Milani and by Pack and Craver. The latter writers prefer this form of treatment to the use of chemical hemolytic agents. Measures directed towards the spleen, such as irradiation and splenectomy, find no justification empirically and in the light of our present conception of erythremia are distinctly contraindicated. The toxic effects of **benzol** generally, and on the white blood corpuscles in particular, make its use very **dangerous**.

Increasing experience attests to the value of **phenylhydrazine hydrochloride** in the treatment of erythremia. The recent reports of Brown and Giffin, Giffin and Conner, Hurwitz and Levitin may be cited. This drug, introduced in 1918 by Eppinger and Kloss, destroys the red blood corpuscles. Although such treatment is symptomatic and only temporary benefit is secured, this form of therapy has so far proved more effective than any measures previously employed. Its use is, however, attended with danger. Its action is slow and, in the doses recommended, is not evident until several days have elapsed. Furthermore, it is slowly eliminated and its action persists for one or two weeks after administration has been stopped.

Giffin and Conner recommend that a total of 1.5 to 3.5 gm. be given by mouth in the course of 7 to 10 days. The daily dose should not be greater than 0.3 gm. and may well be less. Such doses should not be continued for longer than 4 days and may be followed by 0.1 gm. quantities. Treatment should be guided by **frequent blood examinations**. The administration of phenylhydrazine is followed by leukocytosis, increased serum bilirubin, excretion of dark-colored urine and finally a fall in the red cell count and hemoglobin. If the white cell count remains elevated, the dosage should be decreased, and in any event the administration of the drug should be stopped before the red corpuscles reach 5 million. Subsequent dosage depends on the condition of the patient and the blood findings. Frequently a **weekly dose** of 0.1 gm. suffices to maintain a normal blood count.

It cannot be too strongly urged that **energetic treatment with phenylhydrazine** must be **avoided**. There is relatively little danger if caution is observed, but much harm may be done by haste and carelessness. Excessive doses will produce a severe hemolytic anemia and may prove toxic to the liver. Furthermore, thrombosis is more likely to occur following its use. Giffin and Conner caution that it be given only to ambulatory patients and that every effort should be made to keep the already sluggish circulation as free as possible; that extreme

care be observed in patients suffering from arteriosclerosis or advanced visceral lesions as well as in all patients more than 60 years of age.

Acetylphenylhydrazine, which has recently been recommended, is probably less toxic than phenylhydrazine hydrochloride and equally effective (Bodansky).

Prognosis.—The disease is slowly progressive. Death usually results in 6 to 8 years, but a number of patients have lived longer. Death may result from vascular complications such as thrombosis (cerebral, portal, mesenteric) or hemorrhage, or cardiac failure. In a number of patients chronic nephritis with uremia, cirrhosis of the liver or some superimposed infection is the fatal sequel.

Pathology.—The bone marrow is congested, deep red throughout and bloody. Microscopically hyperplasia of the erythropoietic and leukopoietic areas is observed, but such disordered blood formation as is observed in pernicious anemia is conspicuously absent. Other organs are markedly congested and vascular lesions such as hemorrhages, thrombosis and infarcts may be observed.

History.—The first case was described by Vaquez in 1892. The description of 4 cases by Osler in 1903 attracted general attention to this disease.

BIBLIOGRAPHY

Classification of Anemia

- BERGUND, H. AND FALLON, M.: An attempt to classify the anemias, *J. Am. M. Ass.*, 95: 72, 1930.
 WATKINS, C. H.: A classification of chronic idopathic secondary anemia, *J. Am. M. Ass.*, 93: 1365-1367, 1929.
 WINTROBE, M. M.: A classification of anemias on the basis of differences in the size and hemoglobin content of the red corpuscle, *Proc. Soc. Exper. Biol. & Med.*, 27: 1071-1073, 1930.

Posthemorrhagic Anemia

- KEITH, N. M., ROWNTREE, L. G. AND GERAGHTY, J. T.: A method for the determination of plasma and blood volume, *Arch. Int. Med.*, 16: 547-576, 1915.
 ROBERTSON, O. H. AND BOCK, A. V.: Blood volume in wounded soldiers, *J. Exper. Med.*, 29: 139; 155, 1919.

Treatment of Anemia

- AGNEW, G. H.: Blood transfusion; factors frequently overlooked, *Canad. M. A. J.*, 14: 388-391, 1924.
 BARKAN, G.: Therapie der Anamien mit grossen Eisengaben, *Klin. Wchnschr.*, 2: 1748-1751, 1928.
 CARTLAND, G. F. AND KOCH, F. C.: Diet proteins and vitamins as related to hemoglobin production in rats, *Am. J. Physiol.*, 87: 240-261, 1928.
 COHN, E. J., MINOT, G. R., FULTON, J. F., ULRICH, H. F., SARGENT, F. C., WEARE, J. H. AND MURPHY, W. P.: The nature of the material effective in pernicious anemia (I), *J. Biol. Chem.*, 74: 69, 1927.
 ———, ALLEN, G. A. AND SALTER, W. T.: The nature of the material in liver effective in pernicious anemia (II), *J. Biol. Chem.*, 77: 325-358, 1928.
 COLEBROOK, L. AND STORER, E. J.: Immuno-transfusion, *Lancet*, 2: 1841-1844; 1894-1898, 1923.
 CONNERY, JOSEPH E.: The treatment of pernicious anemia with an extract of fish liver, *Am. J. M. Sc.*, 180: 603, 1930.
 DAKIN, H. D., WEST, R. AND HOWE, M.: Further note on a substance in liver active in pernicious anemia, *Proc. Soc. Exper. Biol. & Med.*, 28: 2, 1930.
 DOAN, C. A.: Recognition of biologic differentiation in white blood cells with especial reference to blood transfusion, *J. Am. M. Ass.*, 86: 1593-1597, 1926.
 ———: The transfusion problem, *Physiol. Rev.*, 7: 1-84, 1927.
 DRINKER, C. K. AND BRITTINGHAM, H. H.: The cause of the reactions following transfusion of citrated blood, *Arch. Int. Med.*, 23: 133, 1919.
 DUTTON, W. F.: *Intravenous Therapy*, Philadelphia, F. A. Davis Company, 1924.
 DYKE, S. C.: Liver therapy in secondary anemia, *Lancet*, 1: 1192-1194, 1929.
 ELVBHJEM, C. A. AND HART, E. B.: Relation of iron and copper to hemoglobin synthesis in chick, *J. Biol. Chem.*, 84: 131-141, 1929.
 GIBSON, P. C.: Technique of blood transfusion, *Lancet*, 2: 375-377, 1926.
 ISAACS, R.: The effect of arsenic on the maturation of red blood cells, *Folia Haemat.*, 37: 389, 1928.
 JONES, N. W., PHILLIPS, B. I. AND NOKES, H. T.: Hematopoietic effect of nuclear extracts in experimental anemia and in human anemias, *J. Am. M. Ass.*, 90: 75, 78, 1928.
 ———, LANSSELL, O. AND NOKES, H. T.: The hemopoietic effect of nuclear extracts in human anemias, *Ann. Int. Med.*, 2: 603-621, 1928.
 JOSEPHS, H. W.: The diagnosis and treatment of the anemias of infancy, *Southern M. J.*, 23: 1135, 1930.
 JUBB, LOUIS: Transfusion of pure whole blood, *J. de chir.*, 24: 522-539, 1924.
 KEEFER, C. S., HUANG, K. K. AND YANG, C. S.: Liver extract, liver ash and iron in the treatment of anemia, *J. Clin. Investigation*, 9: 533, 1930.
 KIMPTON, A. R. AND BROWN, J. H.: A new and simple method of transfusion, *J. Am. M. Ass.*, 61: 117, 1913.
 KOESSLER, K. K., MAYRE, S. AND LOUGHLIN, R.: The relation of anemia, primary and secondary to vitamin A deficiency, *J. Am. M. Ass.*, 87: 476-482, 1926.
 LINDBERG, G.: Ueber Anämie nach Influenza nebst einigen Bemerkungen zur Eisentherapie der Anämien, *Acta med. Scandinav.*, 56: 162-187, 1922.

- METTIER, S. R. AND MINOT, G. R.: The effect of iron on blood formation as influenced by changing the acidity of the gastric contents in certain cases of anemia, *J. Clin. Investigation*, 7: 510, 1929.
- and —: The effect of iron on blood formation as influenced by changing the acidity of the gastroduodenal contents in certain cases of anemia, *Am. J. M. Sc.*, 181: 25-36, 1931.
- MILLS, EDWARD S.: The treatment of idiopathic (hypochromic) anemia with iron and copper, *Canad. M. A. J.*, 12: 175-178, 1930.
- MINOT, G. R.: In *Oxford Medicine*, New York, Oxford University Press, 2: 646, 1920.
- AND MURPHY, W. P.: Treatment of pernicious anemia by a special diet, *J. Am. M. Ass.*, 87: 470-476, 1926.
- MITCHELL, H. S. AND SCHMIDT, L.: Iron and nutritional anemias, *J. Biol. Chem.*, 70: 471-480, 1926.
- MURPHY, W. P.: Observations on the treatment of anemia, *Surg. Gynec. Obst.*, 50: 246-250, 1930.
- AND POWERS, J. H.: Value of liver in treatment of anemia due to hemorrhage, *Surg. Gynec. Obst.*, 48: 480-486, 1929.
- MUSSEY, J. H.: Hypodermic injections of iron and arsenic in secondary anemia, *Boston M. & S. J.*, 166: 776-777, 1912.
- : The influence of inorganic iron on the regeneration of blood after hemorrhagic anemia, *Arch. Int. Med.*, 28: 638, 1921.
- MUSSEY, J. H. AND WIRTH, W. R.: Anemia in the South, *Ann. Int. Med.*, 5: 861-869, 1927.
- MYERS, VICTOR C. AND BEARD, HOWARD H.: The influence of inorganic elements on blood regeneration in nutritional anemia, *J. Am. M. Ass.*, 93: 1210-1213, 1929.
- NATHE, K., OCHSNER, A. AND BOITEL, W.: Blood transfusion using Percy's method; hemostatic action of blood transfusion, *Arch. f. klin. Chir.*, 132: 420-469, 1924.
- NICHOLS, ELGIWA A.: Suggestions for the administration of the Minot and Murphy special diet for pernicious anemia, *Boston M. & S. J.*, 196: 302-305, 1927.
- PERCY, N. M.: A simplified method of blood transfusion, *Surg. Gynec. Obst.*, 21: 360-365, 1915.
- RIECKER, H. H., WINTERS, M. E. AND FIELD, HENRY, JR.: Serum iron studies, *J. Clin. Investigation*, 7: 497, 1929.
- ROBSCHT-ROBBINS, F. S.: The regeneration of hemoglobin and erythrocytes, *Physiol. Rev.*, 9: 666-709, 1929.
- SCANNELL, J. M.: Whole blood transfusions, *Long Island M. J.*, 20: 150-157, 1926.
- SCHIFF, E., ELIASBERG, H. AND JOFFE, N.: Kupferbehandlung der Anämie im Säuglingsalt, *Klin. Wchnschr.*, 9: 2144, 1930.
- SCHULTEN: The treatment of hypochromic anemia with large doses of reduced iron, *München. med. Wchnschr.*, 77: 355, 1930.
- SEYDERHELM, R.: Zur Eisentherapie, *Deutsche med. Wchnschr.*, 51: 359-361, 1925.
- SIMMONDS, N., BECKER, J. E. AND MCCOLLUM, E. V.: Relation of vitamin E to iron assimilation, *J. Am. M. Ass.*, 83: 1047-1050, 1927.
- STARKENSTEIN, E.: Neue pharmakologische Richtlinien für die Eisentherapie, *Med. Klin.*, 23: 111-114, 1927.
- SURE, BARNETT, KIK, M. C. AND WALKER, DOROTHY: The effect of avitaminosis on hemopoietic function, *J. Biol. Chem.*, 83: 375-385, 1929.
- UNGER, L. J.: A new method of syringe transfusion, *J. Am. M. Ass.*, 64: 582-584, 1915.
- : Recent simplifications of the syringe method of transfusion, *J. Am. M. Ass.*, 65: 1029, 1915.
- VAUGHAN, J. M.: Liver treatment of anemias, *Quart. J. Med.*, 23: 218-232, 1930.
- WADDELL, J., STEENBOCK, H. AND HART, E. B.: Ineffectiveness of high doses of iron in curing anemia in rat, *J. Biol. Chem.*, 83: 243-250, 1929.
- , ELVEHEIM, C. A. AND HART, E. B.: Further proof that anemia produced on diets of whole milk and iron is due to deficiency of copper, *J. Biol. Chem.*, 83: 251-260, 1929.
- AND HART, E. B.: Specificity of copper as supplement to iron in cure of nutritional anemia, *J. Biol. Chem.*, 84: 115-130, 1929.
- WHIPPLE, G. H.: Experimental anemias, diet factors and related pathologic changes of human anemias, *J. Am. M. Ass.*, 91: 863-867, 1928.
- : Blood regeneration in severe anemia, *Surg. Gynec. Obst.*, 50: 244-245, 1930.
- AND ROBSCHT, F. S.: Iron and arsenic as influencing blood regeneration following simple anemia, *Arch. Int. Med.*, 27: 591-603, 1921.
- AND ROBSCHT-ROBBINS, F. S.: Blood regeneration in severe anemia, *Am. J. Physiol.*, 72: 395-407; 408-418; 419-430; 431-435, 1925; *ibid.*, 79: 260-270; 271-279; 280-288, 1927; *ibid.*, 80: 391-399; 400-410, 1927; *ibid.*, 83: 60-75; 76-83, 1927.
- AND WALDER, G. B.: Blood regeneration in severe anemia, *Am. J. M. Sc.*, 179: 628-643, 1930.
- WILLIAMSON, C. S. AND ETS, H. N.: Value of iron in anemia, *Arch. Int. Med.*, 36: 333-354, 1925.
- WITTS, G. J.: Note on blood transfusion, with account of fatal reaction, *Lancet*, 1: 1297-1299, 1929.

Simple Chronic Anemia

- ALDER, A.: Beitrag zur Kenntnis der Anämien in der Schwangerschaft, *Ztschr. f. Geburt. u. Gynäk.*, 87: 505-518, 1924.
- BLAND, P. B., GOLDSTEIN, L. AND FIRST, A.: Secondary anemia in pregnancy and in puerperium, *Am. J. M. Sc.*, 179: 48-66, 1930.
- BROWN, G. E. AND ROTH, G. M.: The anemia of chronic nephritis, *Arch. Int. Med.*, 30: 817-840, 1922.
- DOUGLAS, A. H. AND TANNENBAUM, H.: The mechanism of secondary anemia, *Arch. Int. Med.*, 45: 248-256, 1930.
- FABER, K.: Anämische Zustände bei der Chronischen Achylia Gastrica, *Klin. Wchnschr.*, 50: 958-962, 1913.
- GRAM, H. C.: A study of the development of pernicious anemia, *Folia Haemat.*, 39: 461-474, 1930.
- KAZNELSON, P., REIMANN, F. AND WEINER, W.: Achylische Chloranämie, *Klin. Wchnschr.*, 8: 1071-1074, 1929.
- KÖHNEL, P.: Untersuchungen über die physiologische Schwangerschaftsanämie, *Ztschr. f. Geburt. u. Gynäk.*, 90, 511-541, 1926.

- METTIER, S. R. AND MINOT, G. R.: The effect of iron on blood formation as influenced by changing the acidity of the gastroduodenal contents in certain cases of anemia, *Am. J. M. Sc.*, 181: 25-36, 1931.
- PEPPER, O. H. P.: A review of our knowledge of the anemias of pregnancy, *M. Clin. N. Am.*, 12: 925, 1929.
- SCOTT, J. M. D. AND BARCROFT, J.: The blood volume and the total amount of hemoglobin in anemic rats, *Biochem. J.*, 18: 1-8, 1924.
- WADDELL, J., STEENBOCK, H. AND HART, E. B.: Ineffectiveness of high doses of iron in curing anemia in rats, *J. Biol. Chem.*, 83: 243-250, 1929.
- WATKINS, C. H.: Classification of idiopathic secondary anemia, *Proc. Staff Meeting Mayo Clinic*, 4: 19-20, 1929.
- WAUGH, T. R.: Hypochromic anemia with achlorhydria, *Arch. Int. Med.*, 47: 71-81, 1931.
- WINTROBE, M. M.: The erythrocyte in man, *Medicine*, 9: 195-255, 1930.
- WITTS, L. J.: Simple achlorhydric anemia, *Guy's Hosp. Rep.*, 80: 253-296, 1930.

Chlorosis

- ASHWELL, S.: Observations on chlorosis and its complications, with 15 cases, *Guy's Hosp. Rep.*, 1: 529-579, 1836.
- CABOT, R. C.: Osier and McCrae, *Modern Medicine*, Ed. 3, Philadelphia, Lea & Febiger, 5: 59, 1927.
- CAMPBELL, J. M. H.: Chlorosis: A study of the Guy's Hospital cases during the last thirty years, with some remarks on its etiology and the causes of its diminished frequency, *Guy's Hosp. Rep.*, 73: 247-297, 1923.
- HALDANE, J. AND SMITH, J. L.: The mass and oxygen capacity of the blood in man, *J. Physiol.*, 25: 831-843, 1900.
- VON HORSSLIN, H.: Zur Abnahme der Chlorose, *München. med. Wchnschr.*, 73: 853-856, 1926.
- MINOT, G. R.: In *Oxford Medicine*, Part II, New York, Oxford University Press, 2: 600, 1920.
- NAEGELI, O.: *Blutkrankheiten und Blutdiagnostik*, Ed. 4, Berlin, J. Springer, 1923.
- ORDWAY, THOMAS AND GORHAM, L. W.: In *Oxford Monographs on Diagnosis and Treatment*, New York, Oxford University Press, 9: 123, 1930.
- PLESCH, J.: Hämodynamische Studien, *Ztschr. f. exper. Path. u. Therap.*, 6: 380-618, 1909.

Aplastic Anemia

- DELAET, MAURICE: La pathologie professionnelle due aux corps radioactifs, *Ann. de méd. lég.*, 8: 443-452, 1928.
- DUKE, W. W.: Aplastic anemia, *J. Am. M. Ass.*, 91: 720-722, 1928.
- EHRLICH, P.: Ueber einen Fall von Anämie, mit Bemerkungen über regenerative Veränderungen des Knochenmarks, *Charité-Ann.*, 13: 300-309, 1888.
- FARLEY, DAVID L.: Depressed bone marrow function from the arsphenamins (including a type of so-called agranulocytosis), *Am. J. M. Sc.*, 197: 214-227, 1930.
- GIBSON, A. G.: Action of adrenalin in aplastic anemia, *Lancet*, 2: 948-949, 1926.
- GRAHAM-ROGER, C. T.: *Industrial Diseases*, Rapid Reference Manual, New York State Department of Labor, Albany, J. B. Lyon, 1924.
- HAMILTON, ALICE: The growing menace of benzene (benzol) poisoning in American industry, *J. Am. M. Ass.*, 78: 627-630, 1922.
- HURWITZ, R. H. AND DRINKER, C. K.: The factors of coagulation in the experimental aplastic anemia of benzol poisoning with special reference to the origin of prothrombin, *J. Exper. Med.*, 21: 401-424, 1915.
- ISAACS, R.: The effect of roentgen ray irradiation on red blood cell production in cancer and leukemia, *Am. J. M. Sc.*, 171: 20-37, 1926.
- KRUMBHAAR, E. B.: Blood and bone marrow in gas poisoning, *J. Am. M. Ass.*, 72: 39, 1919.
- MARTLAND, H. S.: Occupational poisoning in manufacture of luminous watch dials, *J. Am. M. Ass.*, 92: 552; 466, 1929.
- MCCORD, C. P.: The present status of benzene (benzol) poisoning, *J. Am. M. Ass.*, 93: 280-283, 1929.
- MINOT, G. R. AND SPURLING, R. G.: Effect on blood of irradiation, especially short wave length roentgen-ray therapy, *Am. J. M. Sc.*, 168: 215-241, 1924.
- MOORE, J. E. AND KEIDEL, A.: Stomatitis and aplastic anemia due to neoarsphenamin, *Arch. Dermat. & Syph.*, 4: 169, 1921.
- MUSSEY, JOHN H.: Study of a case of aplastic anemia, *Arch. Int. Med.*, 14: 275-288, 1914.
- PAPPENHEIM, A.: Pathologie und Therapie der hämorrhagischen Diathesen und Anämien, *Folia haemat.*, 2: 355-361, 1905.
- SANTÉSSON, C. G.: Ueber Chronische Vergiftungen mit Steinkohlentheerbenzin: vier Todesfälle, *Arch. f. Hyg.*, 31: 836-876, 1897.
- SCHNEIDER, J. P.: Aplastic anemia, *Am. J. M. Sc.*, 156: 799, 1918.
- SELLING, L.: A preliminary report of some cases of purpura hemorrhagica due to benzol poisoning, *Bull. Johns Hopkins Hosp.*, 21: 33-37, 1910.
- STEARNS, A.: *Pernicious Anemia and Aplastic Anemia*, New York, Wm. Wood and Co., 1924.
- UPHAM, J. H. J. AND NELSON, G. I.: Fetal liver feeding in aplastic anemia, *Missouri State M. Ass. J.*, 27: 1-5, 1930.

Pernicious Anemia

- ADDISON, THOMAS: Anaemia: Disease of the suprarenal capsules (meeting of the South London Medical Society, March 6, 1849), *Medical Gazette*, 43: 517-518, 1849. On the Constitutional and Local Effects of Disease of the Supra-renal Capsules. In a Collection of the Published Writings of the Late Thomas Addison, New Sydenham Society, London, J. E. Adlard, 1868.
- ALT, H. L.: Metabolism in pernicious anemia, *Arch. Int. Med.*, 43: 488-503, 1929.
- ASHBY, W.: Effect of treatment on blood volume of patients with pernicious anemia, *Arch. Int. Med.*, 35: 733-739, 1925.

- ASHFORD, BAILEY K.: The anemias of sprue, *Arch. Int. Med.*, 45: 647-673, 1930.
- BAKER, B. M., BORDLEY, J., III AND LONGCOPE, W. T.: Effect of liver and liver extracts on symptoms and signs referable to nervous system in pernicious anemia, *Minnesota Med.*, 13: 815-819, 1930.
- BEIGLER, S. K. AND REESE, H. H.: Subacute combined degeneration of spinal cord and pernicious anemia, *Am. J. M. Sc.*, 171: 194-202, 1926.
- BIERMER, A.: Ueber progressive perniciose Anämie, *Korrespondenzblätter für schweizerische Aerzte*, 2: 15-18, 1872.
- BLASCHY, R.: Efficacy of liver therapy in spinal symptoms of pernicious anemia, *München. med. Wchnschr.*, 77: 183-184, 1930.
- BLOTNER, H. AND MURPHY, W. P.: The effect of liver on the blood sugar level, *J. Am. M. Ass.*, 92: 1332-1336, 1929.
- BUBERT, H. M.: Subacute combined sclerosis, *J. Am. M. Ass.*, 90: 903-906, 1928.
- CAREY, J. B.: Studies in pernicious anemia with especial reference to hereditary factor, achylia, and the presence of abnormal bacteria in duodenal contents, *Minnesota Med.*, 9: 385-391, 1926.
- CASTLE, WILLIAM B.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. I. The effect of the administration to patients with pernicious anemia of the contents of the normal human stomach recovered after the ingestion of beef muscle, *Am. J. M. Sc.*, 178: 748-764, 1929.
- AND BOWIE, M. A.: A domestic liver extract for use in pernicious anemia, *J. Am. M. Ass.*, 92: 1830-1832, 1929.
- AND TOWNSEND, W. C.: Observations on the etiologic relationship of achylia gastrica to pernicious anemia. II. The effect of the administration to patients with pernicious anemia of beef muscle after incubation with normal human gastric juice, *Am. J. M. Sc.*, 178: 764-777, 1929.
- , AND HEATH, C. W.: Etiologic relationship of achylia gastrica to pernicious anemia, *Lancet*, 1: 1062-1063, 1930.
- , AND —: Observations on the etiologic relationship of achylia gastrica to pernicious anemia, *Am. J. M. Sc.*, 180: 805, 1930.
- COHN, E. J., MINOT, G. R., FULTON, J. F., ULRICH, H. F., SARGENT, F. C., WEARE, J. H. AND MURPHY, W. P.: The nature of the material in liver effective in pernicious anemia (I), *Biol. Chem.*, 74: 69, 1927.
- , ALLES, G. A. AND SALTER, W. T.: The nature of the material in liver effective in pernicious anemia (II), *J. Biol. Chem.*, 77: 325-358, 1928.
- COLLIE, J. B.: A method of preparation of a liver extract powder for the treatment of pernicious anemia, *Canad. M. A. J.*, 18: 392-393, 1928.
- CONNER, H. M.: The treatment of pernicious anemia with swine stomach, *J. Am. M. Ass.*, 94: 388-390, 1930.
- : Hereditary aspect of achlorhydria in pernicious anemia. A study of gastric acidity in 154 relatives of 109 patients having pernicious anemia, *J. Am. M. Ass.*, 94: 606-612, 1930.
- CONNERY, JOSEPH E.: The treatment of pernicious anemia with an extract of fish liver, *Am. J. M. Sc.*, 180: 603, 1930.
- COOMBS, C. F.: Cardiac symptoms of pernicious anemia with particular reference to cardiac pain, *Brit. M. J.*, 2: 185, 1926.
- CORNELL, B. S.: A chronic infection with *B. welchii*, *J. Infect. Dis.*, 36: 425-429, 1925.
- : The etiology of pernicious anemia, *Medicine*, 6: 375-417, 1927.
- DAVIDSON, L. S. P.: The etiology of pernicious anemia: A review of the factors concerned in its production, *Edinburgh M. J.*, 35: 322-343, 1928.
- AND GULLAND, G. L.: Pernicious anemia, *St. Louis, C. V. Mosby Co.*, 1930.
- DEWESSELOW, O. L. V. AND BAMFORTH, J.: The blood and plasma volumes in pernicious anemia, *Lancet*, 1: 1066-1068, 1928.
- DOAN, C. A.: Phagocytic cell in pernicious anemia, *J. Exper. Med.*, 43: 289-296, 1926.
- DRAPER, GEORGE: Human Constitution: A Consideration of Its Relationship to Disease, Philadelphia & London, W. B. Saunders Co., 1924.
- ELDER, C.: Tropical sprue and pernicious anemia; etiology and treatment, *Lancet*, 1: 75-77, 1925.
- FINNEY, J. T. M. AND RIENHOFF, W. F.: Gastrectomy, *Arch. Surg.*, 18: 140-162, 1929.
- GOMPertz, L. M. AND COHEN, W.: The effect of smaller doses of histamin in stimulating human gastric secretion, *Am. J. M. Sc.*, 177: 59-64, 1929.
- GRAHAM, D., FARQUHARSON, R., BORSOOK, H. AND GOULDING, A. M.: Urobilinogen excretion in Addison's "pernicious" anemia before and after liver therapy, *J. Clin. Investigation*, 7: 510, 1929.
- GRINKER, R. R.: Pernicious anemia, achylia gastrica and subacute combined degeneration of the cord and their relationship, *Arch. Int. Med.*, 38: 292-302, 1926.
- GULLAND, LOVELL G. AND GOODALL, ALEXANDER: The Blood: A Guide to Its Examination and to the Diagnosis and Treatment of Its Diseases, Ed. 3, Edinburgh, W. Green and Son, Limited, 1925.
- HUNTER, C.: Analysis of 60 cases of gastric anacidity associated mainly with chronic diarrhea and pernicious anemia, *Canad. M. A. J.*, 13: 38-43, 1923.
- HUNTER, W.: Is pernicious anemia a special disease? *The Practitioner*, 41: 81-103, 1888.
- : Specific infective nature of Addison's anemia: its course and treatment, *Brit. M. J.*, 2: 1299, 1907.
- HURST, A. F.: Addison's (pernicious) anemia, and subacute combined degeneration of spinal cord, *Brit. M. J.*, 1: 93-100, 1924.
- : Achlorhydria of Addison's (pernicious) anemia—subacute combined degeneration of cord—Hunterian glossitis syndrome, *Guy's Hosp. Rep.*, 76: 287-293, 1926.
- ISAACS, R.: Systemic relapses during liver induced hemopoietic remissions in pernicious anemia, *Am. J. M. Sc.*, 178: 500-505, 1929.
- , STURGIS, C. C. AND SMITH, M.: Treatment of pernicious anemia, *J. Am. M. Ass.*, 91: 1687-1690, 1928.
- JAMIESON, H. C.: Some historical aspects of pernicious anemia, *Canad. M. A. J.*, 18: 188-192, 1928.
- JOHANSEN, A. H.: Achylia in pernicious anemia after liver treatment, examinations after histamin injections, *J. Am. M. Ass.*, 92: 1728-1730, 1929.
- KREFFER, C. S. AND BLOOMFIELD, A. L.: Significance of gastric anacidity, *Bull. Johns Hopkins Hosp.*, 39: 304-329, 1926.

- KNOTT, F. A.: Addison's anemia: effect of treatment on intestinal infection, *Lancet*, 2: 968-970, 1928.
- KRUMHAAER, E. B.: Thoughts on the morbid processes active in pernicious anemia, *Am. J. M. Sc.*, 175: 523-527, 1928.
- LEEMAN, J. AND MEANS, J. H.: Blood pressure in pernicious anemia, *Am. J. M. Sc.*, 175: 777-791, 1928.
- LICHTHEIM: Zur Kenntnis der perniziösen Anaemie, *Verhandl. d. Kong. f. inn. Med.*, 6: 84-99, 1887.
- MACHT, D. I.: Pernicious anemia: an experimental contribution to the etiology, diagnosis and treatment, *J. Am. M. Ass.*, 89: 753-759, 1927.
- AND ANDERSON, W. T.: Phototherapy in pernicious anemia, *J. Pharmacol. & Exper. Therap.*, 34: 365-389, 1928.
- MACLACHLAN, W. W. G. AND KLINE, F. M.: The occurrence of anemia in four generations, *Am. J. M. Sc.*, 172: 533-543, 1926.
- MCCANN, WM. S.: Effect of kidney on blood regeneration in pernicious anemia, *Proc. Soc. Exper. Biol. & Med.*, 15: 255, 1928.
- McKINLAY, P. L.: Influence of liver treatment on mortality from pernicious anemia, *Lancet*, 2: 1086-1088, 1929.
- : Mortality from pernicious anemia in Scotland: influence of liver treatment, *Glasgow M. J.*, 113: 133-140, 1930.
- MEANS, J. H. AND RICHARDSON, WYMAN: Impressions of nature of pernicious anemia in light of the newer knowledge, *J. Am. M. Ass.*, 91: 923-925, 1928.
- MELLANBY, E.: Diseases produced and prevented by certain food constituents, *J. Am. M. Ass.*, 96: 325-331, 1931.
- METTLER, S. R.: Structural changes of liver in pernicious anemia, *Arch. Path.*, 8: 213-223, 1929.
- MINOT, G. R.: In *Oxford Medicine*, Part II, New York, Oxford University Press, 2: 1920.
- , MURPHY, W. P. AND STETSON, R. P.: The response of the reticulocytes to liver therapy; particularly in pernicious anemia, *Am. J. M. Sc.*, 175: 581-599, 1928.
- MONTGOMERY, E. W.: Studies in pernicious anemia: Outstanding clinical problem and geographical distribution in Western Canada, *Canad. M. A. J.*, 16: 244-250, 1926.
- MORRIS, H. H.: Anemias in China, *China M. J.*, 43: 768-771, 1929.
- MUELENBRACHT, E. AND HOLM, SIGRID: Eosinophilia in liver diet, *Am. J. M. Sc.*, 179: 199-208, 1930.
- MULLER, GULLI LINDB: The relation of cholesterol, lecithin phosphorus and fatty acids to the remission of pernicious anemia, *Am. J. M. Sc.*, 179: 816-837, 1930.
- MCSSEE, J. H.: Clinical manifestations of sprue and relation of the disease to pernicious anemia, *M. Clin. N. Amer.*, 9: 895-908, 1926.
- NAEGELI, O.: *Blutkrankheiten und Blut diagnostik*, Ed. 4, Berlin, Julius Springer, 1923.
- NYE, R. N.: Investigation relative to B. welchii infection of intestinal tract as etiological factor in pernicious anemia, *J. Clin. Investigation*, 4: 71-91, 1927.
- NYFELDT, A.: Experimental pernicious anemia, *Compt. rend. Soc. de biol.*, 94: 608-610, 1926.
- ORDWAY, T. AND GORHAM, L. W.: The treatment of pernicious anemia with liver and liver extract, *J. Am. M. Ass.*, 91: 925-928, 1928.
- PEABODY, F. W.: Bone marrow in pernicious anemia, *Am. J. Path.*, 3: 179-202, 1927.
- PINEY, A.: Recent Advances in Haematology, Ed. 2, Philadelphia, F. Blakiston's Son & Co., 1928.
- PORTER, W. B., WILLIAMS, J. P., FORBES, J. C. AND IRVING, HAZELWOOD: Aqueous extract of liver: development and use in treatment of pernicious anemia, *J. Am. M. Ass.*, 93: 176-179, 1929.
- AND RUCKER, J. E.: The treatment of nontropical sprue with liver extract, *Am. J. M. Sc.*, 179: 310-316, 1930.
- PRICE-JONES, C.: Red cell diameters in one hundred healthy persons and in pernicious anemia; the effect of liver treatment, *J. Path. & Bact.*, 32: 479-501, 1929.
- PULVER, H.: Behebung der Schwierigkeiten bei der Behandlung der perniziösen Anämia mit Leber, *Deutsche med. Wchnschr.*, 55: 99-101, 1929.
- REED, G. B., ORR, J. H. AND BURLEIGH, C. H.: Blood changes in rabbits resembling those in pernicious anemia accompanying B. welchii infections, *Canad. M. A. J.*, 16: 525-531, 1926.
- REZNIKOFF, P.: Rectal administration of liver extract (cod), *J. Am. M. Ass.*, 93: 367-368, 1929.
- RICHARDSON, W.: Pernicious anemia, *New England J. Med.*, 200: 540-545, 1929.
- RIDDLE, M. C.: The endogenous uric acid metabolism in pernicious anemia, *J. Clin. Investigation*, 8: 69-88, 1929.
- : The blood sugar during remission in pernicious anemia, *Am. Inst. Med.*, 8: 1097-1103, 1930.
- : Pernicious anemia, blood regeneration during early remission, *Arch. Int. Med.*, 46: 417, 1930.
- AND STURGIS, C. C.: The effect of single massive doses of liver extract on patients with pernicious anemia, *Am. J. M. Sc.*, 180: 1-11, 1930.
- ROWNTREE, L. G., BROWN, G. E. AND ROTH, GRACE M.: *The Volume of the Blood and Plasma in Health and Disease*, Philadelphia, W. B. Saunders Co., 1929.
- SCHILLING, V.: Experiences with liver therapy in pernicious anemia, *Deutsche med. Wchnschr.*, 55: 1701-1704, 1929.
- SEYDERHELM, R.: Small intestine and pernicious anemia, *Klin. Wchnschr.*, 3: 568-572, 1924.
- , LEHMANN, W. AND WICHELS, P.: Experimental pernicious anemia, *Klin. Wchnschr.*, 3: 1439-1440, 1924.
- : Possibilities and limitations of liver therapy, *Deutsche med. Wchnschr.*, 55: 1704-1706, 1929.
- SHARP, E. A.: An anti-anemic factor in desiccated stomach, *J. Am. M. Ass.*, 93: 749, 1929.
- SNAPPER, I. AND DUPREZ, J. D. G.: Dried stomach of pigs for treatment of pernicious anemia, *Nederl. Tijdschr. v. Geneesk.*, 74: 745-747, 1930.
- STIEGLITZ, E. J.: Disturbances of renal function in pernicious anemia, *Arch. Int. Med.*, 83: 58-70, 1924.
- STOCKTON, C. G.: Long duration of remission in pernicious anemia, *Am. J. M. Sc.*, 158: 471, 1919.

858 DISEASES WITH RED CORPUSCLE ALTERATIONS

- STURGIS, C. C. AND ISAACS, R.: Desiccated stomach in the treatment of pernicious anemia, *J. Am. M. Ass.*, 93: 747-749, 1929.
- AND —: Treatment of pernicious anemia with desiccated defatted stomach, *Am. J. M. Sc.*, 180: 597, 1930.
- TORREY, J. C. AND KAHN, M. C.: Progressive anemia following single intramarrow injection of *Bacillus welchii* toxins, *Am. J. Path.*, 5: 117-140, 1929.
- TSCHERKES, L. A.: Influence of serum from pernicious anemic persons treated by liver on growth of seedlings, *Proc. Soc. Exper. Biol. & Med.*, 26: 869-871, 1929.
- UNGLEY, C. C. AND SUZMAN, M. M.: Subacute combined degeneration of the cord. Symptomatology and effects of liver therapy, *Brain*, 52: 271-284, 1929.
- UPJOHN, L. B., ISAACS, R. AND GUSTAFSON, F. G.: The effects of serums from normal and from anemic persons on the growth of seedlings, *Arch. Int. Med.*, 42: 909-915, 1928.
- WEIL, A. AND DAVIDSON, C.: Changes in the spinal cord in anemia, *Arch. Neurol. and Psych.*, 22: 966-1000, 1929.
- WHIPPLE, G. H.: Pigment metabolism and regeneration of hemoglobin in the body, *Arch. Int. Med.*, 29: 711-731, 1922.
- WILKINSON, J. F.: Pernicious anemia, *Brit. M. J.*, 1: 236-239, 1930.
- WILLIUS, F. A. AND GIFFIN, H. Z.: The angular syndrome in pernicious anemia, *Am. J. M. Sc.*, 174: 30-33, 1927.
- WINTROBE, M. M.: The etiology of pernicious anemia, *New Orleans M. & S. J.*, 80: 446-453, 1928.
- : The hemoglobin content, volume and thickness of the erythrocyte in pernicious anemia and sprue and the changes produced by liver therapy, *Am. J. M. Sc.*, 181: 217-239, 1931.
- WOLTMAN, H. W.: The nervous symptoms in pernicious anemia: an analysis of 150 cases, *Am. J. M. Sc.*, 157: 400, 1919.
- ZADEK, I.: Laboratory findings in pernicious anemia, *Klin. Wchnschr.*, 5: 1331-1334, 1926.
- : Pathogenesis of pernicious anemia: result of postmortem examination of patients who died during remission, *Klin. Wchnschr.*, 8: 1527-1530, 1929.

Hemolytic Anemias

- ALDER, A.: Beitrag zur Kenntnis der Anämien in der Schwangerschaft, *Ztschr. f. Geburtsh. u. Gynäk.*, 87: 505-518, 1924.
- ACBERTIN, C.: L'anémie pernicieuse gravidique, *Presse méd.*, 82: 13-17, 1924.
- BARDENWERFER, H. W.: Ascaris lumbricoides infestation with extreme anemia, *J. Am. M. Ass.*, 91: 1037, 1928.
- BARRON, M.: Infestation with *diphyllobothrium latum* fish tapeworm, with especial reference to native cases, *J. Am. M. Ass.*, 92: 1587-1593, 1929.
- BEAULT, P.: Un cas de guérison d'anémie pernicieuse gravidique avant l'accouchement par ingestion de fole, *Bull. Soc. d'obst. et de gynéc. de Paris*, 17: 619-621, 1928.
- BRILL, I. C.: Acute febrile anemia, *Arch. Int. Med.*, 37: 244-247, 1926.
- CUMMER, CLYDE L.: Anemia and other blood changes in syphilis, *J. Am. M. Ass.*, 91: 689-695, 1928.
- EHRSTRÖM, R.: Zur Frage des gastrointestinalen Ursprungs der perniziösen Anämie, *Ztschr. f. klin. Med.*, 105: 106-117, 1927.
- ESCH, P.: Zur Kenntnis der perniciosoartigen, Graviditätsanämie, *Arch. f. Gynäk.*, 129: 788-801, 1927.
- HOSKIN, T. J. AND CEIRIOG-CADLE, E.: A case of severe anemia of pregnancy simulating Addison's anemia, *Lancet*, 1: 433-434, 1927.
- ISAACS, R., STURGIS, C. C. AND SMITH, M.: Tapeworm anemia, *Arch. Int. Med.*, 42: 313-321, 1928.
- KEGEL, A. H., McNALLY, W. D. AND POPE, A. S.: Methyl chloride poisoning from domestic refrigerators, *J. Am. M. Ass.*, 98: 353-358, 1929.
- LARRABEE, R. C.: Severe anemias of pregnancy and puerperium, *Am. J. M. Sc.*, 170: 371-389, 1925.
- LEDERER, M.: A form of acute hemolytic anemia probably of infectious origin, *Am. J. M. Sc.*, 170: 500-510, 1925.
- : Three additional cases of acute hemolytic (infectious) anemia, *Am. J. M. Sc.*, 179: 228-236, 1930.
- MACINTOSH, A. H. AND CLELAND, J. B.: A case of rapidly increasing anemia with irregular pyrexia and death, *Australian M. Gaz.*, 2: 462-463, 1902.
- MEANS, J. H.: Development of gastric symptoms in a patient totally relieved of pernicious anemia by liver therapy, *New England J. Med.*, 199: 1274-1276, 1928.
- MINOT, G. R.: In *Oxford Medicine*, Part II, New York, Oxford University Press, 2: 640, 1920.
- MOSCHCOWITZ, E.: An acute febrile pleochromic anemia with hyaline thrombosis of the terminal arterioles and capillaries, *Arch. Int. Med.*, 36: 89-93, 1925.
- MURDOCK, T. P.: Hemolytic anemia of pregnancy with reports of cases, *Ann. Int. Med.*, 1: 133-136, 1927.
- NÄGELI, O.: *Blutkrankheiten und Blutdiagnostik*, Ed. 4, Berlin, Springer, 1923.
- PEPPER, O. H. P.: A review of our knowledge of the anemias of pregnancy, *M. Clin. N. Am.*, 12: 925, 1929.
- PETERSON, R., FIELD, H. AND MORGAN, H. S.: Liver treatment in the pernicious anemia of pregnancy, *J. Am. M. Ass.*, 94: 839-842, 1930.
- PINEY, A.: *Recent Advances in Haematology*, Ed. 2, Philadelphia, P. Blakiston's Son and Co., 1928.
- : *Diseases of the Blood*, Philadelphia, P. Blakiston's Son and Co., p. 75, 1928.
- SCHNEIDER, G. H.: Die Stellung der Haematopathia gravidarum in System der Anämien, *Ztschr. f. Geburtsh. u. Gynäk.*, 90: 487-501, 1927.
- SMITH, C. T.: An anemia of the puerperium, *Surg. Gynec. Obst.*, 40: 223-227, 1925.

Sickle Cell Anemia

- BISHOP, F. W.: Elliptical human erythrocytes, *Arch. Int. Med.*, 14: 388, 1914.
- BRANDAU, G. M.: Incidence of the sickle cell trait in industrial workers, *Am. J. M. Sc.*, 180: 813-818, 1930.
- COOLEY, T. B. AND LEE, P.: The sickle cell phenomenon, *Am. J. Dis. Child.*, 32: 334-340, 1926.

- COOLEY, T. B. AND LEE, P.: Sickle cell anemia in a Greek family, *Am. J. Dis. Child.*, 88: 103-106, 1929.
- DRESBACH, M.: Elliptical human red corpuscles, *Science*, 19: 469, 1904.
- FRADKIN, W. Z. AND SCHWARTZ, L. S.: Sickle cell anemia, *J. Lab. & Clin. Med.*, 15: 519-529, 1930.
- GRAHAM, G. S.: A case of sickle cell anemia with necropsy, *Arch. Int. Med.*, 34: 778-800, 1924.
- GUNTHER, H.: Die klinische Bedeutung der Ellipsenform der Erythrozyten, *Deutsch. Arch. f. klin. Med.*, 162: 215-230, 1928.
- HAHN, E. V.: Sickle cell (drepanocytic) anemia with a report of a second case successfully treated by splenectomy and further observations on the mechanism of sickle cell formation, *Am. J. M. Sc.*, 175: 206-217, 1928.
- AND GILLESPIE, E. B.: Sickle cell anemia. Report of a case greatly improved by splenectomy. Experimental study of sickle cell formation, *Arch. Int. Med.*, 39: 238-254, 1927.
- HERRICK, J. B.: Peculiar elongated and sickle-shaped red corpuscles in a case of severe anemia, *Arch. Int. Med.*, 6: 517-521, 1910.
- HUCK, J. B.: Sickle cell anemia, *Bull. Johns Hopkins Hosp.*, 34: 335-344, 1923.
- HUCK, J. G. AND BIGALOW, R. M.: Polkilocytes in otherwise normal blood (elliptical human erythrocytes), *Bull. Johns Hopkins Hosp.*, 34: 390-393, 1923.
- HUNTER, W. C. AND ADAMS, R. B.: Hematologic study of three generations of a white family showing elliptical erythrocytes, *Ann. Int. Med.*, 2: 1162-1174, 1928.
- JOSEPHS, H. W.: Sickle cell anemia, *Bull. Johns Hopkins Hosp.*, 40: 77-84, 1927.
- LANDON, J. F. AND LYMAN, A. V.: Sickle cell anemia: splenectomy, *Am. J. M. Sc.*, 178: 223-228, 1929.
- LAWRENCE, J. S.: Elliptical and sickle-shaped erythrocytes in the circulating blood of white persons, *J. Clin. Investigation*, 5: 31-49, 1928.
- : Human elliptical erythrocytes, *Am. J. M. Sc.*, 181: 240-245, 1931.
- RICH, A. R.: Splenic lesion in sickle cell anemia, *Bull. Johns Hopkins Hosp.*, 43: 398-399, 1928.
- SCHRIER, J. B. AND WAUGH, T. R.: Studies on a case of sickle cell anemia, *Canad. M. A. J.*, 23: 375, 1930.
- SMITH, J. H., JR.: Sickle cell anemia, *M. Clin. N. Amer.*, 11: 1171-1190, 1928.
- STEWART, W. B.: Sickle cell anemia, report of a case with splenectomy, *Am. J. Dis. Child.*, 84: 72-80, 1927.
- SYDENSTRICKER, V. P.: Further observations on sickle cell anemia, *J. Am. M. Ass.*, 83: 12-17, 1924.
- , MULHERIN, W. A. AND HOUSEAL, R. W.: Sickle cell anemia, *Am. J. Dis. Child.*, 26: 132-154, 1923.

Anemias of Childhood

- BLACKFAN, K. D., BATT, J. M. AND DIAMOND, L. K.: *The Anemias of Childhood*, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 9: 531, 1930.
- COOLEY, T. B.: Likenesses and contrasts in the hemolytic anemias of childhood, *Am. J. Dis. Child.*, 36: 1257-1262, 1928.
- AND LEE, P.: A series of cases of splenomegaly in children, with anemia and peculiar bone changes, *Tr. Am. Pediat. Soc.*, 37: 29-30, 1925.
- VON JAKSCH, RUDOLPH: Ueber Leukämie und Leukocytose im Kindesalter, *Wien. klin. Wchnschr.*, 2: 435: 450, 1889.
- : Ueber Diagnose und Therapie der Erkrankungen des Blutes, *Prag. med. Wchnschr.*, 15: 389-403: 414, 1890.
- WHITCHER, B. R.: Erythroblastemia of infants (von Jaksch's disease), *Am. J. M. Sc.*, 179: 230-241, 1930.

Polycythemia

- BLUMENTHAL, R.: Un cas de polycythémie myélogène, *J. med. de Brux.*, 10: 545-554, 1905.
- BODANSKY, M.: Effect of compounds related to hydrazine in producing anhydremia and experimental anemia, *J. Pharmacol. & Exper. Therap.*, 23: 127-133, 1924.
- PROCKBANK, T. W.: Neurologic aspects of polycythemia vera, *Am. J. M. Sc.*, 178: 209-215, 1929.
- BROWN, G. E. AND GIFFIN, H. Z.: Studies of the vascular changes in cases of polycythemia vera, *Am. J. M. Sc.*, 171: 157-168, 1926.
- AND —: Peripheral arterial disease in polycythemia vera, *Arch. Int. Med.*, 40: 703, 1930.
- CHRISTIAN, H. A.: The nervous symptoms of polycythemia vera, *Am. J. M. Sc.*, 154: 547, 1917.
- DETRE, L.: Polycythemia ending in panmyelophthisis, *Med. Klin.*, 22: 1297-1299, 1926.
- DI GUGLIELMO, G.: Eritroleucemia e plastrinemia, *Folia med.*, 6: 35, 1: 81; 101; 55, 1920.
- ENGELKING, E.: Ueber familiäre Polycythämie und die dabei beobachteten Augenveränderungen, *Klin. Monatsb. f. Augenh.*, 64: 645-664, 1920.
- EPPINGER, H. AND KLOSS, K.: Zur Therapie der Polyzthyämie, *Therap. Monatsch.*, 32: 322-326, 1918.
- FITZ, R.: *Polycythemia*, Oxford Medicine, New York, Oxford University Press, 2: 703, 1920.
- GANS, O.: Ueber Spezifische Hautveränderungen bei Erythrämie, *Virchows Arch. f. path. Anat.*, 263: 565-573, 1927.
- GREISBÖCK, FELIX: Die Bedeutung der Blutdruckmessung, *Verhandl. d. Kong. f. inn. Med.*, 21: 97-104, 1904.
- GIFFIN, H. Z. AND CONNER, H. M.: The untoward effects of treatment by phenylhydrazine hydrochloride, *J. Am. M. Ass.*, 92: 1505-1507, 1929.
- HARROP, G. A., JR.: Polycythemia, *Medicine*, 7: 291-344, 1928.
- ILAY, J. AND EVANS, W. H.: Acute eosinophilic leukemia and eosinophilic erythro-leukemia, *Quart. J. Med.*, 22: 167-189, 1929.
- HERXHEIMER, G.: Ueber die Lymphoblasten (grosszellig lymphatische) und Myeloblasten leukämie, *München. med. Wchnschr.*, 60: 2506; 2573, 1913.

860 DISEASES WITH RED CORPUSCLE ALTERATIONS

- HIRSCHFELD, H.: Die Krankheiten des Blutes und der Blutbildenden Organe, Berlin, J. Springer, 2: 259, 1925.
- HURWITZ, S. H. AND LEVITIN, J.: The value of phenylhydrazine in the treatment of polycythemia vera, *Am. J. M. Sc.*, 177: 309-319, 1929.
- ISAACS, R.: Pathologic physiology of polycythemia vera, *Arch. Int. Med.*, 31: 289-296, 1923.
- IZQUIERDO, J. J. AND CANNON, W. B.: Studies on the conditions of activity in endocrine glands, XXIII. Emotional polycythemia in relation to sympathetic and medullary action on the spleen, *Am. J. Physiol.*, 84: 545-562, 1923.
- LANSON, P. D.: The rôle of the liver in acute polycythemia, *J. Pharmacol. & Exper. Therap.*, 7: 169-224, 1915-1916.
- LUCAS, W. S.: Erythremia, or polycythemia with chronic cyanosis and splenomegaly, *Arch. Int. Med.*, 10: 597-667, 1912.
- MAKAREVITCH, O. B.: Case of polyglobulia changing into anemia with leukemoid increase of leukocytes, *Klinicheskaya meditsina*, 7: 1054-1059, 1929.
- MILANI, GUIDO: Roentgen treatment of Vaques's disease, *J. Am. M. Ass.*, 93: 1205-1208, 1929.
- MINOT, G. R. AND BUCKMAN, T. E.: Erythremia (polycythemia rubra vera), *Am. J. M. Sc.*, 166: 469-489, 1923.
- OSLER, W.: Chronic cyanosis with polycythemia and enlarged spleen: A new clinical entity, *Am. J. M. Sc.*, 126: 187-201, 1903.
- PACK, G. T. AND CRAVER, L. F.: Radiation therapy of polycythemia vera, *Am. J. M. Sc.*, 180: 609, 1930.
- PARKES-WEBER, F. AND BODE, O. B.: Polycythemia, Erythrocytosis and Erythremia (Vaques-Osler Syndrome), London, H. K. Lewis and Co., 1929.
- ROWNTREE, L. G., BROWN, G. E. AND ROTH, G. M.: The Volume of the Blood and Plasma in Health and Disease, Philadelphia and London, W. B. Saunders Co., 1929.
- VAQUEZ, M. H.: Sur une forme spéciale de cyanose s'accompagnant d'hyperglobulie excessive et persistante, *Bull. med.*, 6: 849, 1892.
- WINTER, K.: Ueber Polyzythämie mit und ohne Milztumor, *Med. Klin.*, 4: 1017-1023, 1908.
- WINTROBE, M. M.: The erythrocyte in man, *Medicine*, 9: 195-256, 1930.

CHAPTER IV

DISEASES ASSOCIATED CHIEFLY WITH ALTERATIONS IN THE WHITE CORPUSCLES

BY JOHN H. MUSSER, M.D., AND MAXWELL M. WINTROBE, M.D.

- THE LEUKEMIAS**, p. 861—Historical note, p. 861—Definition, p. 861—Varieties of leukemia, p. 861—Etiology, p. 862.
- CHRONIC MYELOID LEUKEMIA**, p. 863—Symptomatology, p. 863—Blood changes, p. 865—Diagnosis, p. 866—Complications and sequelae, p. 866—Prognosis, p. 867—Pathology, p. 867.
- CHRONIC LYMPHATIC LEUKEMIA**, p. 867—Definition, p. 867—Symptomatology, p. 867—Blood changes, p. 869—Diagnosis, p. 869—Complications and sequelae, p. 870—Clinical course, p. 870—Pathology, p. 870.
- THE ACUTE LEUKEMIAS**, p. 870—Definition, p. 870—Classification, p. 871—Etiology, p. 871—Symptomatology, p. 871—Clinical course, p. 871—Blood changes, p. 872—Diagnosis, p. 872—Pathology, p. 873—History, p. 873.
- UNUSUAL TYPES OF LEUKEMIA**, p. 873—Aleukemic leukemia, p. 873—Eosinophilic leukemia, p. 873—Mast cell leukemia, p. 873—Monocytic leukemia, p. 873—Plasma cell leukemia, p. 873—Chloroma, p. 873—Pseudoleukemia, p. 874—Mixed-cell leukemia, p. 874.
- TREATMENT OF LEUKEMIA**, p. 874—Symptomatic, p. 874—Benzol, p. 874—Roentgen ray, p. 875—Radium, p. 875.
- ACUTE BENIGN LYMPHADENOSIS**, p. 876—Definition, p. 876—Terminology, p. 877—Etiology, p. 877—Symptomatology, p. 877—Clinical course, p. 878—Blood changes, p. 878—Diagnosis, p. 878—Treatment, p. 878—Pathology, p. 878.
- GRANULOCYTOPENIA**, p. 879—Agranulocytic angina, p. 879—Symptomatology, p. 879—Laboratory findings, p. 880—Diagnosis, p. 880—Treatment, p. 880—Pathology, p. 880—Etiology, p. 881.

THE LEUKEMIAS

Historical Note.—Hughes Bennett, in 1845, first recognized as a clinical entity a disease in which there was a "suppuration" of the blood attended by enlargement of the liver and spleen, and to which he gave the name "leukocythemia." His clinical description was followed in the same year by the report of Virchow, who described the disease under the name "leukemia," or "white blood." Virchow later recognized the distinction between a type in which lymphatic enlargement predominated and one in which splenomegaly was more marked. The studies of Neumann on bone marrow revealed the "myelogenous" nature of some cases of leukemia. The differential staining methods discovered by Ehrlich made it possible to distinguish the leukemias according to the type of leukocytes involved.

Definition.—Leukemia is a morbid condition characterized by widespread hyperplasia of the leukopoietic tissues, either myeloid or lymphadenoid, throughout the body which is usually associated with qualitative and quantitative changes in the circulating white cells of the blood.

Varieties of Leukemia.—The leukemias are distinguished by certain characteristic clinical changes, notably varying grades of splenic and glandular enlargement, as well as by changes in the blood. Two distinct forms are recognized. First, the *myeloid* type characterized by hyperplasia of the white cells of the marrow (granulocytes) and the appearance of myelocytes and myeloblasts to the extent of from 20 to 40 per cent or more of the total leukocytes present in a given specimen of blood; and second, the *lymphatic* type, in which there is hyperplasia of the lymphatic tissues and a predominance of cells of the lymphocyte series in the blood. As a general principle, it may be affirmed that changes in the maturity of the white corpuscles are of greater significance in

the diagnosis of leukemia than any increase in the number of leukocytes. Furthermore, it may be pointed out that in certain instances marked increases in the number of white corpuscles may take place in response to infection and even numerous immature forms may appear without any characteristic hyperplasia of the leukopoietic tissues. Such "leukemoid" blood pictures are not regarded as true examples of leukemia but rather as instances of abnormal response on the part of the bone marrow. In the last analysis the diagnosis of leukemia depends upon the finding at autopsy of characteristic histologic changes in the tissues.

The myeloid and lymphatic forms of leukemia are readily separable clinically and hematologically if existing in their usual chronic form, but in rare instances they appear in acute forms. In such cases distinction is sometimes very difficult. An acute myeloid leukemia may present what at first appears to be the same blood picture as an acute lymphatic leukemia. Less frequently the latter is mistaken for the myeloid form. In many instances a critical examination of the leukocytes shows the dominant type of cell to be myeloblastic or lymphoblastic. Not infrequently, however, the correct diagnosis is not determined until autopsy has been carried out. In addition to the types already mentioned a number of atypical forms of leukemia are occasionally encountered. These will be discussed subsequently.

Etiology.—Leukemia is widespread throughout the animal kingdom, occurring frequently in mammals and birds as well as in all human races. Acute leukemias occur most frequently during the first five years of life and in the second decade. After the age of twenty-five their incidence is greatly diminished. Chronic lymphatic leukemia has its chief incidence between the ages of forty and sixty; the chronic myeloid type occurs most frequently between the ages of twenty-five and forty-five and is excessively rare in infancy. All varieties may, however, occur at any age. In children the diagnosis is often missed and the occurrence of leukemia in them is far more frequent than was formerly supposed.

Sex.—There is a decided dominance of male incidence in the lymphatic forms, acute and chronic (nearly 2 to 1). In chronic myeloid leukemia the disproportion is less marked, but definite male predisposition is evident and especially marked in patients under twenty-five years of age and in those over forty-five.

Heredity.—No existing evidence justifies the assumption that any hereditary element is operative in leukemia. A familial occurrence has been described in some instances.

The *causation* of leukemia is unknown. Its discussion is unfortunately limited to the consideration of hypotheses and analogies. Because of the similarity of the blood picture in certain instances of infection to that of leukemia, and on account of the resemblance clinically of acute leukemia and fulminating sepsis, it has been suggested that leukemia results from infection. The apparently simultaneous involvement of tissues throughout the body likewise suggests the presence of some chemotactic influence which affects myeloid or lymphatic tissues generally. Furthermore, the transmission of leukemia in fowls by means of a cell-free Berkefeld filtrate of the affected tissues suggests the activity of some toxin or infective virus. On the other hand, no organism or toxin has yet been isolated; the usual channels of entry of infection such as the gastro-intestinal and respiratory tracts are remarkably free of evidence of disease; leukemia has never been known to be transmitted from mother to newly-born child and the instances in which transmission from one individual to another has been suggested are very rare; and finally, as Gulland and Goodall point out, in the leukemias infiltration of organs and tissues occurs which could not likely appear as the result of a chemotactic stimulus.

In many respects the resemblance of the leukemias to neoplastic growths is quite marked and many observers are firm in their opinion that the leukemias represent a form of new-growth. Blood pictures typical of leukemia have been observed in some instances in association with such neoplasms as sarcoma and lymphosarcoma. Cases have been described in which it has been difficult to

differentiate such conditions from leukemia. The resemblance of chloroma to new-growths is most striking. Again, in her observations on the hereditary transmission of tumors in mice, Slye noted that leukemia occurred only in animals that had tumors. On the other hand, such characteristics as infiltration and invasion of neighboring tissues are absent in leukemias, and the leukoblastic tissue found in the liver, spleen, lymph glands and elsewhere is usually regarded as arising from embryonic tissue located there rather than as the result of metastatic dissemination. The necessity of distinguishing between infection and neoplasm, however, may be questioned since the etiology of the latter, after all, is so little understood.

CHRONIC MYELOID LEUKEMIA

Symptomatology.—**ONSET.**—So insidious is the onset of chronic myeloid leukemia that cases are seen almost invariably only when well established and far advanced. The recognition of the disease early is usually wholly an accidental occurrence. The degree to which this disease may advance without causing symptoms severe and troublesome enough to bring the patient to a physician is truly astonishing.

The early symptoms are those of a gradually developing anemia. One encounters chiefly fatigability, subjective sense of weakness and perhaps some breathlessness upon exertion. In certain instances the patient notices a swelling on the left side which is caused by the greatly enlarged spleen, and quite commonly there is a complaint of a weight or a dragging sensation in the same location with or without pain due to perisplenitis.

OUTWARD APPEARANCE OF THE PATIENT.—The outward appearance of the victim of leukemia may be that of perfect health or, at the other extreme, a picture of long continued, progressive ill health is presented. Individuals having a delicate skin may present a heightened color, even a rosy appearance, as the result of weakness of the circulation and instability of the vasomotor system. In these patients, however, emaciation is frequently apparent and closer examination reveals further evidence of ill health. Most commonly the victim of myeloid leukemia is pale and sallow or the skin may show a grayish pallor. Marked weight loss is common and many of these patients present typically a combination of emaciation, slender extremities and the "poached-egg" belly, the last being due to the great enlargement of the liver and spleen together in many instances with the presence of an ascitic accumulation.

The symptoms complained of may be very varied. They may be associated with the general metabolic disturbances and may be those common to anemia. Attention may be directed chiefly to the cardiovascular system, the gastro-intestinal tract, the skin, nervous system or special senses. Hemorrhage may be the first symptom which causes the patient to realize the seriousness of his malady.

GASTRO-INTESTINAL SYMPTOMS.—In some instances these are quite as troublesome as in pernicious anemia and, in addition to anorexia, flatulence and the like, there may be recurring attacks of diarrhea or dysentery most exhausting to the patient and occasionally accompanied by serious hemorrhages. The enlarged spleen and liver may be the cause of much discomfort both because of their weight and on account of pressure on other organs.

The *spleen* is usually markedly enlarged before the patient presents himself to the physician and the tumor should present few difficulties with respect to diagnosis. The entire course of the development of the splenomegaly may be painless, but not infrequently there is a history of more or less distress in the left upper abdominal quadrant or in the back. Infarcts in the spleen and perisplenitis may occur and give rise to such pain and tenderness as to suggest the presence of some abdominal emergency.

The spleen is smooth and hard. Its characteristic shape is retained and the notches in the border are readily felt. The size of the spleen may be extreme and the organ may extend to the ilium, the umbilicus and even to the right anterior superior spine. If there has been a recent infarct there may be tenderness and a friction rub may be felt or heard,

The size of the spleen varies greatly from week to week, day to day, and even from hour to hour, and a failure to recognize this fact has been responsible for certain false conclusions as to the efficacy of certain lines of treatment. The size does not appear to be related to the total number of white corpuscles.

The Liver.—The liver is demonstrable and usually a decided enlargement is readily detected. The edge is firm and smooth, making palpation easy and often permitting its detection by inspection.

Ascitic accumulations are common in the advanced stages of the ailment.

CARDIOVASCULAR SYSTEM.—Dyspnea, palpitation and ready fatigability may arise at first on account of the splenic tumor, but later cardiac dilatation occurs as the result of anemia. Effort dyspnea may become excessively troublesome. Enlargement of the heart may be detected on examination and systolic murmurs are frequently present. Gravity edema is present almost invariably in the later stages, and general edema with a special tendency to serous accumulations, oftentimes abrupt in onset, in the peritoneal, pleural and other serous cavities may occur.

PULMONARY SYSTEM.—Cough is a common symptom in many cases in which the disease is well established and this may be due to chronic bronchitis or in the later stages to pulmonary congestion or actual edema. Pleurisy with or without effusion, or actual pneumonia are present in some cases. The association of cough, slight fever and loss of weight may suggest in some instances the presence of tuberculosis.

SKIN AND LYMPH GLANDS.—Itching of the skin is an occasional complaint. Leukemic infiltration of the skin is exceptionally rare in myeloid leukemia. Ketron and Gay were able to find only 3 cases in which a histologic examination had been made. They describe an interesting case of their own. Petechiae and hemorrhages are unusual early in the disease, but most decided purpuric manifestations may be present in the later stages, and with these in some instances there is an associated tendency to sudden large hemorrhages into the peritoneal or pleural cavities.

Only in rare instances and in the terminal stages is there any decided glandular involvement and the massive enlargement of abdominal and mediastinal glands reported occasionally must be an exceedingly rare occurrence.

HEMORRHAGE.—In some instances attention is first directed to the serious condition of the patient by the occurrence of a severe hemorrhage. Late in the disease hemorrhage is frequent. The loss of blood in such cases may occur from any mucous membrane with or without obvious and direct irritation or injury. The amount lost may be very large and in terminal cases may result directly in death, though, as a rule, the hemorrhage ceases or is controlled only to be repeated again and again until the patient dies from this added cause of exhaustion and inanition.

UROGENITAL SYSTEM.—Aside from the fact that uric acid is present in excess and that the usual signs of chronic renal congestion may be present in terminal cases with marked myocardial weakness, there is little of importance to be observed clinically. A trace of albumin and an occasional hyaline and granular cast are common findings and in such instances the amount of urine is likely to be diminished.

Menorrhagia, metrorrhagia or amenorrhea not uncommonly occur in women. Priapism, so much stressed in earlier writings as a symptom of leukemia, is an unusual occurrence.

BONES.—Pain and tenderness over the long bones are not encountered very frequently. Craver noted that sternal tenderness, however, was present in 75 per cent of the cases of myeloid leukemia that he observed. Our experience bears out that of Craver. The tenderness is usually limited to a small portion of the sternum, most often the gladiolus or opposite the fifth costal cartilage and the patient is frequently unaware of any point of tenderness until pressure is made at the proper point. It is of great interest that this sign appears to vary with the severity of the illness. One of our patients was able to detect the need for further treatment by a return of the sternal tenderness for which he

had learned to look. Sternal tenderness is much less frequent in lymphatic leukemia.

METABOLISM.—Metabolism is increased greatly and patients frequently show a marked preference for room temperatures too low for the comfort of their attendants or family members. Loss of weight, increased appetite and other manifestations of increased basal metabolic rate may be present. Riddle and Sturgis found that the increased rate was roughly proportional to the severity of the leukemic process and that the pulse rate, the height of the white blood count and the percentage of young myeloid cells were directly correlated with the basal metabolic rate. Irradiation was followed by a transitory rise which lasted about 3 days and then the rate returned to normal, where it remained for 3 to 6 months in patients who were benefited by the treatment. Patients in the terminal stages of the disease continued to have an elevated metabolism despite treatment. Increased consumption of oxygen by the excessive number of white blood cells, increased demand for oxygen by the overactive tissues which are responsible for the production of the large numbers of white cells and, as Riddle and Sturgis suggest, the increased rate of destruction of these cells are probably all factors in the elevation of the metabolism in myeloid leukemia.

SPECIAL SENSES.—True optic neuritis or markedly impaired vision are seldom encountered, but changes due to extravasation of blood or to leukocytic accumulations forming small growths are comparatively frequent complications. Commonly the ophthalmoscopic findings are small, irregular, red-bordered, whitish flecks lying along the vessels at the periphery of a pale fundus. Retinal detachment, clouding of the lens and hemorrhage into the vitreous may occur. Borgeson and Wagener found retinal changes in 87 per cent of cases of myeloid leukemia. Hemorrhage in the retina was more common than in the skin, subcutaneous tissues and mucous membranes.

Cases of deafness are not uncommon and are probably due to hemorrhages. In some instances they assume the form of Ménière's syndrome; indeed, hemorrhage into the labyrinth has been reported in a number of instances.

NERVOUS SYSTEM.—Involvement of the nervous system, although unusual, may assume a variety of forms. Hemorrhage or leukemic infiltration may produce symptoms and signs which indicate the cerebral hemisphere, internal capsule, spinal cord, the nerve roots or ganglia as the seat of disease. Epidural leukemic masses may cause compression of the cord, facial palsy may result from infiltration of the seventh cranial nerve, herpes zoster may arise from leukemic infiltration of the ganglia or sensory nerve roots, symptoms and signs may resemble the nerve changes typical of pernicious anemia, or apoplexy may be the cause of death (Barker, Fried, Rosenkranz).

BLOOD CHANGES.—In a well advanced case one is often struck by the thickness of the blood and the difficulty in making smears because of the stickiness of the blood. In the early stages anemia is absent or slight, but later moderately severe anemia may be present and cause the blood to appear pale. The anemia is of the microcytic type. Anisocytosis is usually present and in the severe stages there are distinct alterations in the size and shape of the red corpuscles. Polychromatophilia is common at such times and normoblasts are often numerous. Macroblasts are much less common. Stippling may be present and reticulocytes are usually increased in number.

Well marked leukocytosis is the rule, the counts ranging between 100,000 and 800,000 cells per c.mm. or higher. A count of 400,000 or thereabouts is most usual. There is a marked increase in the relative number of white cells of the granular series, but more striking than this, and of greatest importance, is the presence of many immature cells not normally seen in the blood. The characteristically important cell in chronic myeloid leukemia is the neutrophilic myelocyte, which occurs in such numbers as to constitute 20 or in certain instances 40 or 50 per cent of the total leukocytes present. Eosinophilic and basophilic myelocytes also occur and occasional myeloblasts are encountered. The latter cells are frequently confused with cells of the lymphocytic or monocytic series.

Every transition between the myeloblast and the multilobed polymorpho-

nuclear leukocyte may be observed. The majority of the leukocytes are polymorphonuclear neutrophils, which are increased absolutely and frequently relatively as well (25 to 75 per cent). Eosinophils are increased so as to maintain or perhaps exceed in many instances their normal ratio and almost invariably are absolutely increased. Basophil granules may occur in either eosinophilic or neutrophilic polymorphonuclear cells. Basophils are commonly observed and may be greatly increased in number (3 to 20 per cent). They are more numerous in myeloid leukemia than in any other disease. The lymphocytes are increased but their percentage is usually relatively low. Monocytes are at first increased in number but later become less evident.

The total number of white cells present is of some importance in indicating the severity of the case. Under treatment with the roentgen ray or radium, benzol and the like, or after the onset of some intercurrent acute infection, even though this be of short duration, the total white count may be reduced to nearly or quite normal. It should be borne in mind, however, that although the total number of leukocytes may be low or normal, prognosis may be grave in the presence of a low count. In such instances immature forms are most numerous.

Blood platelets are usually normal in number or slightly increased in the early stages of the disease. Minot and Buckman stated that wherever there occurred, through the intervention of treatment or otherwise, a rise of platelets from a definitely subnormal number, or a fall from an excessively high level to a normal one, clinical improvement followed, provided the alteration in the leukocytes was also towards the normal. A persistently low count, unchanged by a remission of the disease, often indicated a fatal outcome. Extreme reduction was associated with various types of hemorrhage.

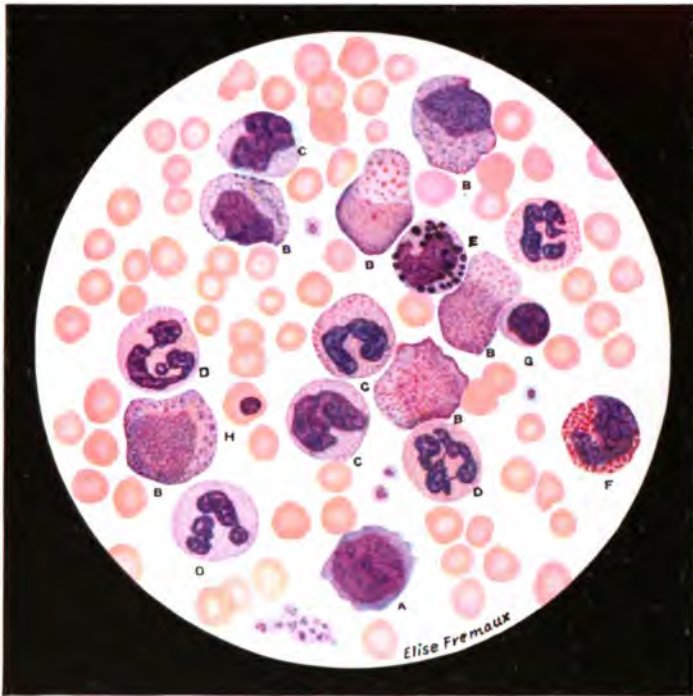
The volume of blood in myeloid leukemia is definitely high, according to Rowntree, Brown and Roth. The increase is due to augmentation both of plasma and cells. This increased volume, they suggest, may be related to the splenomegaly.

Diagnosis.—From the foregoing discussion it is obvious that the diagnosis of chronic myeloid leukemia should be perfectly simple in nearly every instance for any one of adequate training and possessed of proper laboratory facilities. The blood picture usually is striking and absolutely clear in its meaning. The enlargement of the spleen in association with the blood picture makes a diagnostic combination present in no other ailment. Although very rarely symptoms such as progressive loss of weight and abdominal tumor and the finding of red blood corpuscles in the urine may suggest a kidney tumor, physical examination should very readily reveal the identity of the tumor mass. Infarction of the spleen or perisplenitis should cause no confusion if a complete examination is made.

Occasionally the blood picture may be atypical. The white cell count may be normal or there may even be leukopenia. Such counts may follow infection or too energetic therapy or may be associated with spontaneous remission. Even in such cases, however, evidence will be found to suggest bone marrow abnormality. What may cause greater difficulty in diagnosis is the hyperleukocytosis occasionally encountered, particularly in children, as the result of infection or hemorrhage. In such cases the clinical picture is usually quite different. Furthermore, eosinophilic and basophilic cells are not likely to be found and there will usually be a smaller percentage of immature cells. In children the syndrome described by von Jaksch, *anemia pseudoleukemica infantum*, may present some resemblance to leukemia, but it should be remembered that chronic myeloid leukemia is extremely rare at this age.

Myeloma, metastatic carcinoma of the bone marrow, and even more rarely Hodgkin's disease and Banti's disease may be associated with a "leukemoid" blood picture. Piney and Krumbhaar have discussed this subject at some length.

Complications and Sequelae.—Aside from hemorrhage and the symptoms indicative of myocardial insufficiency, there are few complications in any way peculiar to or usually associated with chronic myeloid leukemia. Tuberculosis may become active and pursue an acute miliary or chronic progressive course, and any one of the acute infections may be superimposed accidentally upon a leukemia. It should be remembered that the onset of any acute infec-



CHRONIC MYELOID LEUKEMIA.

Fig. A.—Wright's stain. $\times 950$. *a*, myeloblast; *b*, neutrophilic myelocytes; *c*, neutrophilic metamyelocytes; *d*, polymorphonuclear neutrophils; *e*, basophilic metamyelocyte; *f*, eosinophilic metamyelocyte; *g*, lymphocyte; *h*, normoblast.

PLATE X

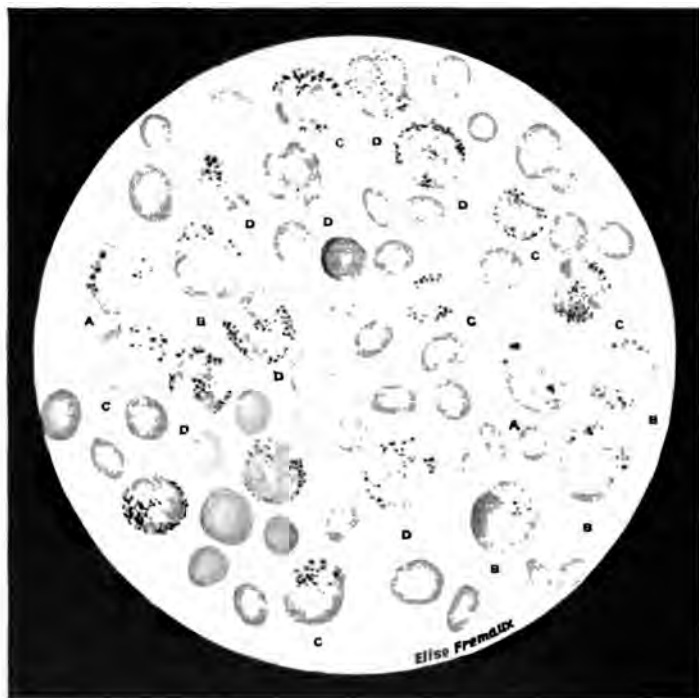


Fig. B.—Peroxidase stain (Goodpasture's). $\times 950$. *a*, early myelocyte; *b*, myelocytes; *c*, metamyelocytes; *d*, polymorphonuclears.

tion such as pneumonia, typhoid, influenza or one of the acute exanthemata may produce a very marked temporary amelioration in the leukemic manifestations. This change may be so marked as to bring the blood findings almost to normal, but is of short duration and in some instances such a remission is followed by a change in the type of the disease, which, formerly chronic and sluggish in its progress, may become acute and progressively fatal.

Prognosis.—The course of chronic myeloid leukemia is slowly progressive and death results usually in 1 to 3 years, although some patients have been kept alive and in moderate or good health for 5 or 10 years under appropriate therapy. Remissions occur and these may be spontaneous, induced by therapy or may follow an acute infection as already mentioned. In such instances symptoms are alleviated or may entirely disappear, red cells and hemoglobin increase, white cells diminish and the spleen becomes smaller. Even in such remissions, however, some evidence of disease, such as a few immature cells, remains evident. Unfavorable signs are a rapid aggravation of symptoms with the onset of marked weakness and fever, and a drop in the number of platelets with the onset of hemorrhage. Death may result from intercurrent infection, progressive anemia, heart failure with general anasarca, hemorrhage or a combination of such causes.

Pathology.—**BONE MARROW.**—The bone marrow in this disease appears at autopsy in most instances pale pinkish or yellowish gray and relatively firm in texture. In rarer instances it carries a greenish tint. It is crowded with cells of all varieties, both leukocytic and erythrocytic, known to this region except the megakaryoblast, although the predominating cell of the intense hyperplasia is the myeloid leukocyte.

THE HEART.—There are no changes in the heart characteristic in themselves of chronic myeloid leukemia, but degenerative changes are extremely common and fatty degeneration is very often present and occasionally extreme. Within the heart one often finds at autopsy yellowish-white growths which, because of the great number of contained leukocytes, suggest a mixture of pus with the fibrin. Microscopical examination may reveal leukocytic infiltration, and in certain unusual instances thrombosis of the coronary branches may cause areas of softening (myomalacia cordis).

THE SPLEEN.—The spleen usually is enormously enlarged, its weight varying from 2 to 18 or 20 pounds. The normal splenic outline is in great measure preserved. Its consistence is firm, its surface smooth, and the normal color is usually changed to a grayish tint. Under the knife it cuts with difficulty because of the great increase of fibrinous tissue in its stroma. Hemorrhagic infarctions are not uncommon. On microscopic examination the splenic tissue is found to resemble the bone marrow in appearance, being filled with an enormous number of cells which consist chiefly of myelocytic forms with either eosinophil or neutrophil granules.

LIVER.—This organ is markedly enlarged in most instances and its capillaries contain large groups of myeloid cells similar to those found in the spleen and bone marrow.

CHRONIC LYMPHATIC LEUKEMIA

Definition.—Chronic lymphatic leukemia is a disease of unknown causation characterized by widespread hyperplasia of the lymphatic tissues throughout the body which is manifested chiefly in glandular enlargement, splenomegaly and usually a marked increase in the relative and absolute numbers of lymphocytes in the blood.

Etiology.—The etiology of this disease has already been discussed in preceding pages.

Symptomatology.—The onset of lymphatic leukemia of the chronic type is usually gradual and insidious, few cases being recognized during the earlier stages. As a rule, there has been an antecedent enlargement of the lymphatic glands or a swelling of the tonsils may have been noticed. Not infrequently the patient does not present himself until increasing weakness and fatigability force him to do so. This seldom occurs until the anemia as well as the char-

acteristic leukocytic changes has become quite marked. These patients ordinarily show a simple pallor, though they are occasionally sallow or gray.

LYMPH GLANDS.—In most instances all accessible glands are found to be affected in some degree or become so during the course of the illness. The glands of the cervical chains are most prominent ordinarily, but on examination the axillary and inguinal glands as well will be found enlarged. Furthermore, glands not usually enlarged in other conditions with which lymphatic leukemia might be confused, are not infrequently enlarged in the latter condition. These glands include the postauricular, submaxillary, epitrochlear and pectoral group of axillary glands. Abdominal glands may be occasionally felt and enlargement of the mediastinal glands also occurs. In certain of the acute cases particularly, the enlargement of the superficial glands may not be excessive though the internal groups of glands may take on rapid and extreme enlargement and produce symptoms of a grave and even fatal character.

The enlargement of the glands is usually moderate in degree but the tumors may vary from a few millimeters to several centimeters in diameter. Rarely are the huge masses seen in Hodgkin's disease or lymphosarcoma encountered. The glands are discrete, firm (but not stony hard), freely movable and not attached to the skin or surrounding tissue. Unless secondary infection has supervened, there is no evidence of inflammatory changes such as redness, pain or tenderness. In exceedingly rare instances glandular enlargement is slight or absent in chronic lymphatic leukemia.

Pressure symptoms are unusual, but occasionally in advanced cases or in acute cases with rapid and extreme enlargement of the internal glandular groups the symptoms of pressure may be extreme and, especially in such cases as show marked mediastinal growths, a horrible picture of death by chronic slowly progressive suffocation is presented.

Enlargement of the tonsils may be a relatively early symptom and leads to unfortunate results through incautious operative procedure.

Very rarely the breast or the salivary and lacrimal glands may be involved and present symmetrical painless enlargements (Mikulicz's syndrome). Thirteen such cases have been described in the literature according to Rowe, who has recently added another.

SKIN LESIONS.—These may be very troublesome symptoms and any one or more of a large group may be present during the course of the disease. Urticaria, pruritis and prurigo may prove especially troublesome, but in addition to these, vesicular, pustular, petechial and nodular lesions, as well as infiltrations, hematomata and actual tumor formations, may occur. Rarely the entire skin may be involved, producing the so-called "universal leukemia cutis." Leukemic infiltration of the face may produce a leonine appearance. Lesions show on section typical leukemic lymphocytic infiltration. In association with these skin manifestations the blood may remain normal for many years or show only moderate changes.

GASTRO-INTESTINAL SYMPTOMS.—These may be marked, moderate or in large part absent and take the form usual in anemia, namely, flatulence, epigastric oppression, anorexia, nausea or perhaps vomiting or diarrhea. In addition, there may be serious hemorrhage from the stomach or bowel as the result of leukemic infiltration of the stomach or intestines. Ascites may be encountered in the later stages.

SPLEEN.—The spleen is moderately or decidedly enlarged but so far as the outward symptoms go the glandular changes dominate the clinical picture as a rule. The spleen ordinarily does not descend more than one or two fingers' breadth below the costal margin and the huge enlargement so common in myeloid leukemia is very rarely encountered in this disease.

THE LIVER.—The liver is usually firm in consistency and moderately enlarged, but in some instances the organ is tremendous in size.

HEART AND LUNGS.—No specific changes occur but, as in myeloid leukemia, a profound myocardial decompensation may be induced and pleurisy and pericarditis occur.

GENITO-URINARY SYSTEM.—Irregularities of menstruation may occur in



CHRONIC LYMPHATIC LEUKEMIA (WRIGHT'S STAIN). $\times 950$. SHOWING THE EXCESSIVELY LARGE NUMBER OF SMALL LYMPHOCYTES.

women. The urine usually contains albumin and casts, although nephritis is rather infrequent. Uric acid excretion is not increased to the extent common in chronic myeloid leukemia. Bence-Jones proteinuria has been reported in several cases (Boggs and Guthrie).

OSSEOUS SYSTEM.—Tenderness of long bones is uncommon. Craver found tenderness of the sternum much less frequent in chronic lymphatic leukemia than in myelogenous leukemia.

SPECIAL SENSES AND NERVOUS SYSTEM.—Disturbances of vision are of unusual occurrence, but "leukemic retinitis" and retinal hemorrhages may occur. Rarely leukemic infiltration of the eyelids or sclerae has been observed. Deafness seldom results from lymphoid involvement of the labyrinth. Only rarely do specific lymphomatous deposits or growths occur in the animal cord or brain.

METABOLISM.—Fever is absent or only slight in degree and in general is proportional to the acuteness of the condition. Krantz and Riddle found that the basal metabolic rate was increased when the disease had progressed far enough to produce more than local symptoms. The increase was not closely related to the height of the white cell count but was slightly correlated to the number of immature forms.

BLOOD CHANGES.—Red corpuscles and hemoglobin may be normal or only moderately reduced until the late stages of the disease. The total leukocyte increase, while definite and striking (the average lying between 200,000 and 250,000 per c.mm. of blood), is seldom as marked as in leukemia of the myeloid type. Platelets are characteristically decreased in number and the degree of decrease, according to Minot and Buckman, serves to indicate the amount of marrow insufficiency. Fluctuations such as occur in chronic myeloid leukemia are unusual.

The blood smear lacks the diversity of form and type in the white and red cells alike which is so characteristic of myeloid leukemia. Nucleated red cells are rather rare and anisocytosis, poikilocytosis, polychromatophilia or stippling are seldom very marked. There is a striking uniformity in the white corpuscles, 90 to 99 per cent being small lymphocytes. While apparently identical with the normal lymphocyte, close examination of these cells reveals certain differences in staining. Many possess only a tiny rim of light blue cytoplasm while other lymphocytes appear to be entirely devoid of cytoplasm. Azure granules are scanty in the cytoplasm that may be seen, and the nuclei often stain more lightly and reveal a looser chromatin network than is seen in the normal small lymphocyte. There may be some variation in the size of the lymphocytes. Large lymphocytes with indented nuclei (Rieder cells) are not infrequently found. Immature lymphocytes occur less commonly. None of these cells show granulation on staining by the peroxidase method.

Diagnosis.—In the majority of instances diagnosis is very readily made. The combination of the outward symptoms of anemia, progressive weakness and fatigability, enlargement of accessible lymphatic glands and spleen, and a blood picture showing clearly a large increase in the number of leukocytes present and an absolute dominance of lymphocytes, is so striking that there is usually little excuse for error when all features are noted. When either the clinical findings or the blood picture alone is considered, difficulty may sometimes be encountered.

Clinically there may be some confusion with glandular tuberculosis, Hodgkin's disease or lymphosarcoma. Tuberculous glands tend to soften and become adherent to the skin. Hodgkin's disease usually commences in one group of glands, frequently the posterior cervical, and generalization occurs only late in the disease. The masses are larger than is common in lymphatic leukemia and more frequently cause pressure symptoms. There may be recurring attacks of fever, weakness and pain. Histological examination of an excised gland reveals a characteristic picture. Lymphosarcoma commences in a localized area, invades the surrounding tissue spaces, forms large masses and spreads by metastasis. The glands are not distinct and the liver and spleen are rarely involved. It is only very rarely indeed that there is the least resemblance in the blood pictures of these diseases and chronic lymphatic leukemia. In the latter disease, furthermore, lymphatic infiltration in the skin, eyelids, pharynx and larynx may be

encountered, whereas such findings are never noted in Hodgkin's disease or lymphosarcoma.

Not infrequently, and particularly in children, a lymphatic reaction may be caused by infection. In whooping-cough marked relative and absolute lymphocytosis is not infrequently encountered. The clinical distinction is readily made. Cabot has described a lymphatic response as the rare result of sepsis. Acute benign lymphadenosis (infectious mononucleosis) may be confused more particularly with acute leukemia. The relative lymphocytosis of granulocytopenic conditions should cause no confusion. Real difficulty may arise when leukocytosis is absent in chronic lymphatic leukemia.

Complications and Sequelae.—The chief complications of chronic lymphatic leukemia relate to the effects of pressure and the occurrence of hemorrhage; otherwise there are no conditions which are worthy of specific mention.

Clinical Course.—The progress of chronic lymphatic leukemia is much slower than that of chronic myeloid leukemia, the average duration being 5 years or longer. Aleukemic forms in which the white cell count is low despite spleen and lymph gland enlargement may be very benign. Remissions in the course of the disease may arise spontaneously or follow treatment or some intercurrent infection. Infections which call forth an increase in the granular leukocytes have a particularly beneficial effect. Favorable signs in the blood are absence of anemia and of large immature and atypical lymphocytes and the occurrence of normal azurophil granules in the lymphocytes present.

Chronic lymphatic leukemia is ultimately fatal. Sepsis, hemorrhage or some complication may cause the end or there may be progressive glandular enlargement, increasing anemia and rapidly progressive weakness and cachexia with death from heart failure or exhaustion.

Pathology.—**GLANDS.**—As might be expected from the clinical discussion of this disease, the dominant feature in the postmortem findings in chronic lymphatic leukemia is the glandular enlargement which is practically universal and of a degree readily recognizable. The glands vary greatly in size but seldom exceed that of a large English walnut. The outline of the gland is usually maintained and there is seldom manifest any tendency to fusion.

On section the gland appears soft and gray or pinkish-gray in color, smooth and homogeneous. The tissue is packed with lymphocytes which are dominantly of the small type and not only fill the vascular spaces but infiltrate the surrounding tissues.

SPLEEN.—The spleen almost invariably shows decided enlargement in chronic lymphatic leukemia but does not reach the enormous dimensions so characteristic of the chronic myeloid form of this disease. Its consistence is variable, the acquisition of any decided firmness in texture depending apparently upon the longer or shorter duration of the disease. Infarcts are met with frequently but the surface of the spleen itself is smooth and the normal outline is preserved. The substance of the organ is filled with infiltrating lymphoid cells and the microscopic structure is thereby rendered almost unrecognizable.

BONE MARROW.—As in the case of chronic myeloid leukemia the bone marrow is gray or grayish-red in color, dense and usually homogeneous. Microscopically it shows almost complete replacement of the normal erythroblastic and myeloblastic tissue by lymphoid cells.

LIVER.—The liver is usually definitely and often greatly enlarged but the only characteristic feature is the collections of lymphocytes forming perivascular nodules in the connective tissue.

Leukemic deposits may be found in various tissues of the body including the meninges, integument, trachea, larynx, the nerves themselves and the kidneys. The tonsils are usually enlarged, as might be expected from the clinical history of the case, and there is lymphocytic infiltration throughout the intestinal tract.

THE ACUTE LEUKEMIAS

Definition.—Acute leukemia is a rapidly progressive and fatal disease of unknown causation characterized by a relatively sudden onset, fever, marked prostration, a tendency to necrotic and gangrenous processes in the mucous mem-

branes of the mouth and throat, hemorrhages in the skin and from mucous membranes, and a blood picture of which the noteworthy features are the presence of large numbers of immature leukocytes, severe and progressive anemia, and frequently leukocytosis. Enlargement of the spleen, lymph glands or liver is not invariably encountered clinically, but infiltration of these organs as well as of the bone marrow by excessive numbers of immature leukocytes is the characteristic postmortem finding.

Classification.—Depending upon the character of the immature cells found in the blood, two types of acute leukemia are distinguished: (a) acute myeloid or myeloblastic leukemia; and (b) acute lymphatic leukemia. A third type, acute monocytic leukemia, has been described by Schilling but most hematologists, notably Naegeli, consider this a form of myeloblastic anemia. Clinically these types of leukemia cannot be differentiated.

Etiology.—Acute leukemia is very rare after 25 years of age, most cases described in adults usually representing an acute exacerbation of a chronic leukemia. Early observers recognized only a lymphatic form of acute leukemia, but later studies have shown that acute myeloid leukemia is the more common of the two types.

Symptomatology.—The onset of acute leukemia may in some instances not be such as to cause immediate anxiety, but frequently the disease is ushered in by symptoms of great gravity and its course is one of dramatic suddenness. There may be some preceding infection, such as tonsillitis. Suddenly marked prostration, fever, headache and general malaise appear and the onset of some severe, malignantly virulent form of sepsis is suspected. In other cases intractable bleeding from the nose, bladder, uterus or bowel may be the first indication of ill health. Generally it may be said that the onset of acute leukemia may suggest the commencement of a large number of diseases among which may be mentioned tonsillitis, quinsy, diphtheria, Vincent's angina, typhoid fever, septicemia of any cause, and purpura haemorrhagica.

Whatever be the mode of onset, a rather typical clinical picture soon develops. The patient appears very ill and is noticeably pale in spite of the associated fever. The mentality is usually clear but delirium and coma may supervene. The exhaustion is profound, the pulse rapid and labile. Petechiae, purpuric spots or even large hemorrhagic areas may appear early or later in the course of the disease. Not infrequently the gums are swollen, red and spongy. Ulcerations, necrosis and even gangrene may be found in the mouth or throat where, it may be noted, Vincent's organisms are commonly encountered. The tonsils are usually enlarged and may be included in the noma-like ulceration. The cervical lymph nodes are also enlarged as a rule, but death often supervenes before any other lymph glands become markedly affected. Pulmonary congestion is not infrequent and there may be pleural effusion. The heart presents the usual signs of anemia. Slight enlargement of the liver and spleen may be encountered but this is by no means invariable. There may be tenderness in the bones and this may be particularly noted in the sternum. Fever is high and irregular.

Instead of presenting the symptoms described, the clinical picture of acute leukemia may be quite misleading and attention may be directed to such systems as the gastro-intestinal, or to the bones and joints or the special senses. Vomiting, severe diarrhea and hemorrhage from the bowel may occur. Disturbances of vision or deafness may result from retinal or labyrinthine hemorrhages and even symptoms of cerebral hemorrhage may be encountered.

A most suggestive association of symptoms which at once indicates a blood examination if this has not already been made, is the combination of fever and a rapidly produced and striking pallor which appears even though loss of blood may be slight or not evident.

CLINICAL COURSE.—The course of acute leukemia is usually stormy and resembles that of an extremely grave and acute infectious disease, death occurring in a few days to a few weeks. Rarely a transient remission may occur and life may linger for several months. Crawford and Weiss in a recent paper called attention to what they term a subacute form of leukemia with insidious onset and a gradual course of several months. Such a case clinically resembles typhoid

fever or subacute bacterial endocarditis. The ultimate outcome, as in the chronic forms of leukemia, is fatal.

BLOOD CHANGES.—If examination be made very early, little anemia may be discovered but in the course of the disease the red cells and hemoglobin drop rapidly and soon a profound anemia is produced. The red corpuscles may show no marked variation from the normal or there may be moderate anisocytosis and slight variation in the shape of the cells. Normoblasts are uncommon but polychromatophilia and stippling occur and even a picture simulating pernicious anemia has been described. Blood platelets are characteristically reduced in number and with this thrombocytopenia all the other phenomena encountered in thrombopenic purpura become manifest. The addition of the factor of blood loss to the already grave cause of anemia, namely, leukemic infiltration of the bone marrow, greatly aggravates the resulting anemia.

A white cell count, particularly in the early stages of acute leukemia, may be quite misleading. At such a time the count is rarely high and even normal or subnormal values may be found. The number of leukocytes usually does not exceed 25,000 or 30,000 per c.mm. early in the disease. It may never be found greater than this, although as a rule there is a rapid rise to 100,000 cells or more. The extreme counts of chronic leukemia are rare and a subnormal total count may persist throughout the course of the disease.

The blood smear reveals the presence of a large number of immature mononuclear leukocytes. At first glance these may be taken for large lymphocytes. Much experience is required in identifying these immature cells, and it is on the nature of these cells as well as on the autopsy findings that the differentiation of acute myeloid and acute lymphatic leukemia rests.

In *acute myeloid leukemia* these mononuclear cells form 30 to 60 per cent of the leukocytes. The most immature forms, the myeloblasts, may be 10 to 20 μ in diameter. These cells possess round or oval nuclei and deep blue cytoplasm which contains no granules. The nuclear chromatin is very fine and is not condensed about the edges so as to form a nuclear membrane. Within the nucleus 4 or 5 rather indistinct nucleoli may be discerned. Besides myeloblasts, premyelocytes and, in lesser numbers, myelocytes may be seen. The latter are easily distinguished by the presence of many cytoplasmic granules. The premyelocytes represent an intermediate stage between myeloblast and myelocyte. They contain a few fine neutrophilic granules which are most useful for diagnosis since they can be demonstrated by the peroxidase test. Neutrophilic polymorphonuclear leukocytes are scanty and eosinophilic and basophilic forms are usually absent.

In *acute lymphatic leukemia* the large mononuclear cells form 50 to 90 per cent of the total. These cells, which are chiefly lymphoblasts, are distinguished from myeloblasts by their coarse or "stippled" chromatin, dense nuclear membrane and prominent nucleoli. Only 1 or 2 nucleoli are found in each nucleus. Further assistance in differentiation is afforded by the perinuclear clear zone which can usually be noted in the cytoplasm of all cells of the lymphatic series. Cells which are more mature than lymphoblasts will also be encountered in acute lymphatic leukemia. Few polymorphonuclear leukocytes are found but an occasional myelocyte may be observed.

It is obvious that the differentiation of acute myeloid and acute lymphatic leukemia is most difficult if not in some cases impossible even for the most practiced eye. The peroxidase test in some instances is of value. This test is positive only when granules are present in the cells examined and is therefore of value in distinguishing premyelocytes and myelocytes from other mononuclear cells. It must be borne in mind, however, that a negative peroxidase test does not rule out myeloid leukemia since myeloblasts do not give this reaction.

Diagnosis.—Clinically acute leukemia may suggest a large variety of conditions among which may be mentioned fulminating sepsis, purpura haemorrhagica, scurvy, ulcerative stomatitis, systemic Vincent's angina, quinsy, noma, diphtheria, granulocytopenic angina and endocarditis. Examination of the blood will readily distinguish acute leukemia from these diseases. In purpura haemorrhagica few or no immature leukocytes are encountered nor are the lymph glands and spleen enlarged. In granulocytopenic angina, anemia and



FIG. A.—ACUTE LEUKEMIA (LYMPHATIC) (WRIGHT'S STAIN). $\times 950$.

a, Lymphoblasts; b, young lymphocytes; c, adult lymphocytes; d, polymorphonuclear neutrophil; e, normoblast.

PLATE XII



FIG. B. Acute Myeloid Leukemia. (Wright's stain, $\times 950$.) (a) myeloblasts; (b) early myelocyte or premyelocyte; (c) and (d) myelocytes, (c) being the younger of the two; (e) juvenile neutrophil; (f) segmented neutrophils; (g) adult lymphocyte; (h) macroblast with diffuse basophilia.

thrombocytopenia are absent or relatively slight and the lymphocytes present are mature forms. Acute benign lymphadenosis (infectious mononucleosis) may cause confusion in the early stages, but the less severe course, the relative mildness of the throat lesions, the absence of marked anemia or reduction in the number of platelets, and the lack of a hemorrhagic diathesis are distinguishing characteristics. Differences in the appearance of the lymphocytes encountered in this disease and in acute lymphatic leukemia are considered in the discussion of acute benign lymphadenosis.

Pathology.—The postmortem findings in *acute myeloid leukemia* vary only slightly from those encountered in the chronic form save that the changes such as would require greater time for their development are more prominent in the latter than in the former ailment. There is diffuse hyperplasia of myeloid leukopoietic tissue in the marrow, lymph glands, liver and spleen. These changes are so great as to amount to a definite transformation, but histologic study is required to determine whether or not the proliferation is one of myeloid or lymphatic tissue. The application of the oxydase test to the tissue may be of great value.

In *acute lymphatic leukemia* instead of excessive numbers of myeloblasts, premyelocytes and myelocytes, the infiltrations in the bone marrow, spleen, lymph glands, liver and other organs are found to be composed of lymphocytes, the majority of which are immature forms.

History.—In 1857 Friedreich reported a case of acute leukemia, but it was not until 1889, when Ebstein's paper appeared, that any extensive account of the symptoms of this disease was presented. The conception that all acute leukemias are lymphatic in type was based on Fraenkel's studies, and it was not until 1905 that the myeloid character of many cases of acute leukemia was recognized by Aubertin.

UNUSUAL TYPES OF LEUKEMIA

Aleukemic Leukemia.—This term is used to refer to those types of leukemia, myeloid or lymphatic, in which the total white cell count remains normal. The condition is in other respects identical with the more usual form of leukemia and is identified by the qualitative changes in the blood and the leukemic changes in the tissues.

Eosinophilic Leukemia and Mast Cell Leukemia.—These rare types of leukemia differ from myeloid leukemia only in that eosinophilic or basophilic leukocytes, respectively, rather than neutrophilic cells form a large proportion of the white corpuscles observed.

Monocytic Leukemia.—This condition was described by Reschad and Schilling in 1913, and since then by several other writers (*vide* Dameshek), as a form of acute leukemia which is distinct from myeloid or lymphatic leukemia and is characterized by the presence in excessive numbers of true monocytes. In many of the cases reported the cells have been subsequently identified as myeloblasts. Most hematologists, among them Naegeli, consider this so-called monocytic leukemia to be myeloblastic (myeloid) leukemia.

Plasma Cell Leukemia.—This is a variant of lymphatic leukemia, acute or chronic, in which a certain proportion of the pathologic cells in the blood, and particularly in the leukemic infiltrations in the tissues, are plasma cells.

Chloroma (Chloroleukemia).—Though formerly considered a new-growth, this condition is now regarded to be an unusual form of leukemia. It is characterized by the occurrence of localized tumors in relation particularly to the periosteum and ligamentous structures of the skull, paranasal sinuses, orbits, spine, ribs and sacrum. These growths may cause protrusion of the eyeball, with diplopia and loss of vision, deafness and other cranial nerve palsies as well as other phenomena caused by pressure or infiltrative growth. The course of the illness is in other respects similar to that of acute leukemia and the blood changes are indistinguishable. Although earlier observers regarded the abnormal cells in the blood and tissues to be lymphatic in origin, it is noteworthy that in the more recent studies which have been favored by better technic, myeloid cells have

been described and many hematologists now even deny the occurrence of lymphatic forms of chloroma.

The tumors are characterized by a peculiar greenish coloration which may be evident on superficial examination or only on sectioning the masses. The cause of this coloration is not known. The other pathologic changes in chloroma are identical with those found in acute leukemia. Brannan recently collected 129 cases from the literature and added 18 new cases.

Pseudoleukemia.—This is a term loosely applied to conditions which resemble leukemia clinically or in which leukemic tissue changes are found without any characteristic blood picture. The term is of no value since it includes cases of true leukemia as well as instances of tumors of lymphoid or marrow tissue, and should therefore not be employed. Likewise the term *leukanemia* should be discarded since it was applied to cases in which the differentiation between myeloid leukemia and pernicious anemia could not be readily made and therefore does not refer to a true clinical entity.

Mixed-cell Leukemia.—This term was given to certain cases in which both granular and nongranular immature leukocytes were found and which were erroneously believed to represent a combination of myeloid and lymphatic leukemia. It is now known that the lymphocyte-like, nongranular cells are really myeloblasts, forms which are very numerous in acute myeloid leukemia or in an acute exacerbation of chronic myeloid leukemia. The cases in which a preëxisting typical picture of myeloid leukemia became transformed to one of apparent lymphatic leukemia as the terminal stage was reached are now explained by the identification of the confusing cells as myeloblasts.

THE TREATMENT OF LEUKEMIA

There is no specific treatment for leukemia. Some of the measures that are employed may alleviate the symptoms for a varying length of time, but none have been conclusively shown to offer any marked effect in prolonging life measures. The **general measures** already described in the discussion of the treatment of anemia should be followed, and particular stress should be given to adequate rest, appetizing food, pleasant surroundings and the relief of any symptoms that may arise. Of the measures more directly concerned with anemia, **blood transfusions** are probably the most valuable and this is the only form of therapy that may have even a slight effect on the acute forms of leukemia. Arsenic was formerly widely employed in the treatment of leukemia but its use cannot be said to have been followed by any beneficial results which might not have occurred without it. **Splenectomy** is distinctly contraindicated. Iron may be administered and liver may be included in the diet, but since the anemia here depends on the disordered activity of the leukopoietic system, little can be expected from the use of measures which do not influence the leukocytes themselves.

Of the measures employed for their effect on the white corpuscles, **benzol, roentgen rays and radium** may be mentioned. **Benzol**, formerly very popular, is now little employed. Its use originates with the observations of Selling, already described, concerning the toxic effects of this substance on the blood. Benzol is a powerful leukocytic poison, powerful for good or for evil according to the method and manner of its use and the response of the individual patient. It is administered in capsules with olive oil. The initial daily dose is 2 gm., given orally in 4 doses of 0.5 gm. each and the maximum of 4 or 5 gm. daily is reached during the course of one week. This amount is continued until the leukocyte count is 30,000 per c.mm., until toxic symptoms appear or an unfavorable influence on the other elements of the blood is suspected. Headache, vertigo, bladder irritability, impotence, gastric disturbances and evidence of renal congestion may occur and demand immediate cessation of administration. One of the great disadvantages of benzol is that its toxic effect is not limited to leukocytes, but blood platelets and red corpuscles may be destroyed as well. These effects have already been described in the discussion of aplastic anemia. It is very important, therefore, to closely follow the **red cell count and platelet count**, as well as the **leukocyte count**, when benzol is being administered. Over-

dosage should be carefully avoided and the possibility of a cumulative after-effect watched for.

In favorable cases the administration of benzol is succeeded by a slight increase in the number of leukocytes and later a striking diminution, chiefly of the polymorphonuclear cells. If favorable effects continue, the pathologic types of white cells tend to disappear and a normal differential leukocyte count is attained. Furthermore, as the white cell picture improves the number of red corpuscles and the amount of hemoglobin rise (Billings). The drug is much more valuable apparently in the myeloid form of leukemia than in cases of the lymphatic type. Improvement of the blood condition is usually attended by a more or less parallel favorable change in the spleen, liver and lymphatic glands. The remission thus induced is, however, only temporary and may soon be followed by a rapidly fatal relapse.

Radiation, in the form of roentgen rays, radium, mesothorium or thorium X, is now more favored than benzol because its effects are less dangerous to the patient. A comparison of the results of radiation of the spleen and over the bones favors the former method, and some investigators state that the latter is inadvisable because of a possible stimulation of leukopoiesis or an inhibitory effect on erythropoiesis (Ordway and Gorham). As is the case with benzol, radiation is more valuable in chronic myeloid than in the lymphatic form and is entirely valueless and even dangerous in the acute forms.

The use of roentgen ray irradiation in the treatment of leukemia is based chiefly on the observations of Bécélère. Bécélère found that such treatment when properly carried out was followed by a return to a normal blood picture, clinical improvement with regained weight, strength and color, and a reduction in the size of the liver and spleen. Health was maintained in some instances for 3 to 6 years but eventually death followed as the result of cachexia, thrombosis or some cardiac, pulmonary or renal complication.

In employing roentgen rays in the treatment of leukemia it is advisable to follow the so-called "cross-fire system" by which maximum deep effect is secured with minimum skin injury. By radiating from different angles of the body it is possible to give 5 or more times the dosage that could safely be given if treatment were carried out at one point only. The use of screens or filters to check the less penetrating and skin-irritating rays affords an additional advantage. McAlpin and Sanger, in summarizing their results from this form of treatment, caution against overdosage and stress the importance of frequent blood counts as a check on the effects of treatment. They found a reduction in the basal metabolic rate to be a good prognostic aid.

Roentgen ray treatment has not been favored by all observers and as many as 50 per cent of refractory cases have been reported. However, improvements in apparatus and in the technic of application should afford much better results.

Radium is now more favored than any other form of treatment. Ordway has outlined the following technic: The radium is completely enclosed in screens or filters of lead, 2 to 3 mm., or brass, 1.2 mm., in thickness. These metals intercept the alpha and soft beta rays which cause irritation of the skin and permit the hard beta and the gamma rays to pass through. By wrapping the radium thus enclosed in 15 or 20 thicknesses of filter paper and gauze, the secondary rays from the lead are intercepted.

The principle of cross-fire and deep therapy is employed. The spleen is outlined and marked, this marking being later traced on thin cotton cloth in which the patient's abdomen is snugly swathed. A series of small squares, a little larger than the size of the radium case, is marked out and each of these is numbered. It is thus possible to apply the radium to successive areas without causing too much skin irritation at any one point over the spleen. The applications should not be placed too close together as the intervening skin may be burned from the double dosage it would thus receive. If the swathe of cotton cloth is well fitted and marked so that it will not be displaced, the adhesive may be applied to it instead of to the skin, much discomfort thus being avoided.

One hundred mg. of radium element or 100 millicuries of radium emanation may be applied in this manner over successive areas of 2 by 2 cm. for 4 to 6

hours. Such long exposures are possible because with the method of filtering advised only 5 per cent of the total activity of the radium is employed. The series of applications may be repeated in 4 to 6 weeks, the time interval depending on the blood and the skin reaction.

As a consequence of this treatment the white cell count will be found to fall, and particularly the immature leukocytes will disappear. Hemoglobin and number of red cells return towards normal, only slight anisocytosis and moderate relative lymphocytosis persisting. As Ordway and Gorham state, the patient, a pale, emaciated, anxious-looking individual with a strikingly prominent abdomen, becomes plump, strong and apparently well. Such a remission usually takes place after about 3 courses of treatment.

Unfortunately the effects of radium treatment are only temporary, relapse takes place, and the response to subsequent radiation is less prompt. In comparison with roentgen ray therapy Ordway and Gorham state that favorable reactions from radium treatment are more prompt and fewer instances of toxic symptoms are encountered. They caution that too frequent and too intensive treatment may be followed by fatalities.

Radiation, whether in the form of roentgen ray or radium, should be stopped when the white cell count has reached 25,000 to 30,000 cells per c.mm. The dosage required to attain these figures must be worked out in each individual case. A blood count should be made 24 hours after the radiation (not at once) and then, if the white cell count has not been sufficiently lowered, when the count is, or has again risen to, about 80,000 cells or higher, radiation may be repeated, the dose this time being somewhat larger. It is important to commence treatment before the relapse has continued too far. A slight or moderate increase in the number of white corpuscles is, however, not in itself an indication for treatment. Leukocyte counts can serve only as rough guides, and, as Krantz and Riddle have emphasized, the patient rather than the white cell count should be treated. Pressure symptoms from enlarged glands or great splenomegaly are indications for treatment. An aggravation of symptoms, particularly when these are symptoms of elevated energy exchange and there is an increase in the basal metabolic rate, suggests the need for treatment even when the white cell count is fairly low, and certainly when the count is 100,000 per c.mm. or still higher. Even in the presence of leukopenia, radiation may be employed if the basal metabolic rate is elevated and pressure symptoms are marked. Isaacs states that irradiation stimulates the primitive hemoblasts to reproduce and causes the older leukocytes to finish their life history, when they die or are excreted. Consequently leukopenia may simply indicate very rapid excretion rather than bone marrow aplasia as it is usually interpreted. Treatment is particularly dangerous when the bone marrow is markedly involved, anemia is marked and blood platelets are significantly reduced in number. In the presence of an unusually large number of immature forms and other signs suggesting an acute relapse in the course of a chronic leukemia, much caution should be employed and not infrequently treatment at such a time is valueless. In the presence of diabetes or nephritis particular care in treatment is necessary.

The technic and results of mesothorium and thorium X therapy are similar to those of radium. It may be found that some cases will respond to one form of radiation when another type seems to have no influence. Occasionally benzol may be beneficially used if other methods have failed. Concerning the influence of radiation in general on chronic leukemia, it may be said that although life may not be prolonged greatly as a rule, marked symptomatic benefit very frequently is attained.

ACUTE BENIGN LYMPHADENOSIS

(Acute Infectious Mononucleosis)

Definition.—The name acute infectious mononucleosis is usually applied to an acute infection, benign in nature and of unknown etiology which is characterized clinically by irregular fever, sore throat, swelling of the lymph glands, notably the cervicals, and enlargement of the spleen, as well as by an absolute

and relative lymphocytosis and the presence in the blood of abnormal, though chiefly mature, lymphocytes.

Terminology.—The name most commonly employed, infectious mononucleosis, is misleading since it suggests that this disease is characterized by the presence of monocytes in the blood. The designation "acute lymphadenosis," suggested by Downey and McKinlay, is inadequate since the benign nature of this condition as distinguished from the fatal outcome of acute lymphatic leukemia, another acute lymphadenosis, is not indicated. For this reason the name "acute benign lymphadenosis" is here employed. The term "glandular fever" is sometimes used as synonymous with acute benign lymphadenosis, but since this implies the etiologic identity of two conditions which are not accepted by all investigators as being one and the same, this designation cannot be employed in the light of the present ignorance concerning the etiology of these conditions.

Etiology.—The occurrence of a lymphocytic reaction resembling leukemia but followed by recovery was recognized as early as 1907 by Türk. Similar cases were reported in subsequent years by Lüdke, Marchand, Cabot and others, but it was not until the report of Sprunt and Evans which appeared in 1920 that much interest in English-speaking countries was aroused. A number of studies, among which may be mentioned those of Longcope, Downey and McKinlay, Bloedorn and Houghton, and Cady, followed.

Nothing is known concerning the etiology of this condition. It occurs sporadically, chiefly in young adults and, judging by the total number of reports, is quite rare. More frequent blood examinations in cases presenting the clinical syndrome of irregular fever, sore throat, cervical adenopathy and splenomegaly will probably reveal more instances of this condition. That it is a clinical entity is suggested by the fact that the same individual may respond to a subsequent infection of another type by the usual increase in polymorphonuclear leukocytes. Sprunt and Evans cite such a case. Staphylococci, streptococci and particularly spirilla and fusiform bacilli of Vincent have been found in smears from the throat lesions. Gorham, Smith and Hunt have reported 3 cases of typical acute benign lymphadenosis developed apparently through contact. Even more interesting is their successful reproduction of the blood picture of this condition in guinea pigs by the inoculation of material taken from the pharynx of these cases, as well as by the injection of living and dead vibrios of Vincent.

The similarity of acute benign lymphadenosis to the epidemic glandular fever of Pfeiffer has been stressed by a number of observers. The latter condition occurs chiefly in children and is characterized by irregular fever, nontender cervical adenopathy, abdominal pain and enlargement of the spleen and liver. Polymorphonuclear leukocytes may be increased in the first few days of the fever but lymphocytosis, both relative and absolute, is characteristic of the disease. Guthrie and Pessel, Gilbert and Coleman, and others have described such epidemics. Tidy and Daniel, in particular, stress the similarity of epidemic glandular fever and acute benign lymphadenosis. Downey and McKinlay, however, point out that the latter does not occur in epidemic form, it is characterized by severe throat symptoms which are usually absent in glandular fever, and furthermore, the characteristic cytology of acute benign lymphadenosis has not been conclusively shown to be present in the epidemic disease of children.

Symptomatology.—The onset of acute benign lymphadenosis is similar to that of any acute infection and is characterized by such complaints as fever, malaise, sore throat, headache, swelling of glands or gastro-intestinal symptoms. A certain amount of toxemia is common. There is an irregular fever which attains 101° to 104° F. The axillary and inguinal glands are usually swollen as well as the cervical nodes. These glands vary in size from that of a pea to that of a walnut. They are firm, discrete and do not suppurate. Slight tenderness may occasionally be present but pain does not occur. Pharyngitis and tonsillitis are frequent, and this inflammation may vary from mild congestion to exudation and ulceration. The latter are more common. The spleen is palpable in about 50 per cent of cases and occasionally the liver may be felt. Hemorrhages in the

skin and mucosa occurred in two of Downey and McKinlay's cases but were not associated with marked anemia. Platelet counts were not recorded.

CLINICAL COURSE.—The irregular fever persists for 1 or 2 weeks and subjective symptoms disappear in 2 or 3 weeks. Adenopathy, splenomegaly and the characteristic blood findings may persist for some time, even for several months. Relapses occasionally take place. There are no known complications although it may be here mentioned that Tidy and Daniel noted hemorrhagic nephritis in 6 per cent of their cases of epidemic glandular fever. No fatalities have been reported.

BLOOD CHANGES.—Red corpuscles and hemoglobin are apparently not influenced by this disease. Leukocytosis is the rule, the majority of counts ranging between 12,000 and 20,000, although as many as 48,000 white cells per c.mm. have been reported. A relative and absolute reduction in the number of granulocytes and a marked increase in the number of nongranular cells is a characteristic feature of the differential white cell count.

The mononuclear cells are of three types: (1) small lymphocytes; (2) large mononuclear leukocytes or monocytes; both of these appear normally in blood; (3) large mononuclear leukocytes which are not normally observed in the blood. The last cells are characteristic of acute benign lymphadenosis and appear in large numbers.

The abnormal cells vary much in size and shape. They possess a nucleus which may be oval, kidney-shaped or slightly lobulated and cytoplasm which most frequently is nongranular and vacuolated or foamy in appearance. The nuclear chromatin forms a coarse network of strands and masses and is not clearly differentiated from the parachromatin. These cells have been identified as highly differentiated, mature lymphocytes. They do not show granules when stained by the peroxidase method and are thus differentiated from monocytes and cells of the granulocytic series.

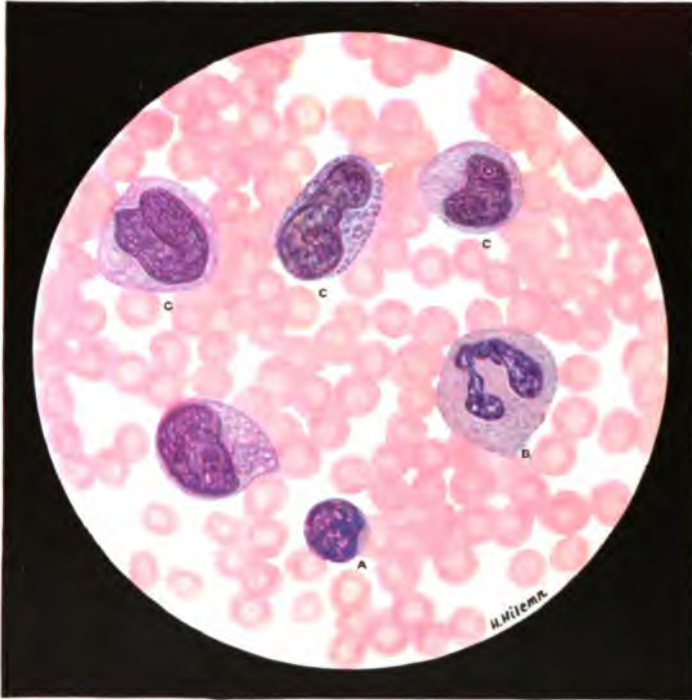
Downey has described two other types of abnormal lymphocytes but these are not found in acute benign lymphadenosis as frequently as the "Type I" cells just described. Type II cells are less varied but larger than the "Type I" cells, their nuclear chromatin is not as condensed, and their cytoplasm is more homogeneous and not vacuolated. Type III cells show some resemblance to the cells of lymphatic leukemia. Their nuclei are diffusely vacuolated and possess 1 or 2 nucleoli. The cytoplasm of the "Type III" cells is likewise vacuolated and may be quite basophilic.

For a complete account, illustrated by an excellent plate, of the hematologic aspects of this disease, the reader is referred to the paper of Downey and McKinlay.

Diagnosis.—Acute benign lymphadenosis may be taken for tonsillitis or simple pharyngitis and very rarely for diphtheria, Vincent's angina, Hodgkin's disease, tuberculous adenitis or syphilis, and even acute leukemia or granulocytopenic angina may be suspected. Examination of the blood readily serves to differentiate these conditions in most instances. A diagnosis of acute leukemia should not be made in the absence of red cell changes, platelet reduction, hemorrhagic phenomena and immature leukocytes. Granulocytopenic angina can be distinguished by the marked leukopenia and granulocytopenia, the severity of the ulceration and toxemia and the rapid course.

Treatment.—The treatment of this disease is similar to that of any acute infection. Mouth gargles such as diluted hydrogen peroxide, sodium perborate or potassium chlorate may be employed. If the spirilla and bacilli of Vincent are found, *neocaraphenamine* (5 per cent in glycerin) may be applied locally.

Pathology.—The benign nature of this disease has not permitted complete studies of the tissues to be made. In lymph glands simple hyperplasia of the type which occurs in nonsuppurative adenitis has been noted by several observers. Fox, carrying out supravitral staining methods, found that the cells in the lymph glands were lymphoid in origin and not monocytes.



ACUTE BENIGN LYMPHADENOSIS (WRIGHT'S STAIN). $\times 950$.

a, Small lymphocyte; *b*, polymorphonuclear neutrophil; *c*, predominating types of cells seen in acute benign lymphadenosis.

GRANULOCYTOPENIA ("AGRANULOCYTOSIS")

The term *granulocytopenia* signifies a reduction below normal in the number of white corpuscles of the granular series, namely, the polymorphonuclear cells, myelocytes and myeloblasts. Granulocytopenia may be quite marked and is usually accompanied by leukopenia. Reduction in the number of white corpuscles of other types such as lymphocytes and monocytes may be associated, and less frequently reduction in the number of blood platelets and red corpuscles may take place. *Agranulocytosis*, strictly speaking, refers to an increase in nongranular leukocytes.* The term is, however, frequently employed incorrectly to signify a reduction in the number of granulocytes and more specifically has been used in referring to a syndrome described by W. Schultz in 1922.

Granulocytopenia is an unusual form of reaction on the part of the bone marrow which is observed in cases of poisoning by certain toxic agents, in certain "blood diseases," and appears also as a rare manifestation associated with sepsis.

The toxic action of benzol, thorium, roentgen rays, arsenic and other substances on the bone marrow has already been discussed. Benzol, in particular, exerts a toxic effect on the granulocytic white corpuscles. Leukopenia may become severe and frequently the blood platelets and red corpuscles are also reduced in number so that an aplastic anemia is produced. The therapeutic use of roentgen rays and radium may be followed by a temporary and, more rarely, a permanent granulocytopenia. The clinical picture in these cases may resemble that of a severe septic infection or the course may be subacute and progressive, as has already been described under the head of aplastic anemia.

A moderate absolute reduction in the number of granulocytes is found in pernicious anemia, sprue and not unusually in chronic posthemorrhagic anemia. A marked reduction is a feature of idiopathic aplastic anemia. In severe septicemia due to a large variety of causes, granulocytopenia and leukopenia may ensue. Farmakidis has recently described such a blood picture in 7 cases of diphtheria. Rarely marked granulocytopenia is noted in other acute infectious diseases such as typhoid, measles, mumps, influenza, malaria, typhus and dengue.

In 1922, Schultz describes a syndrome of unknown etiology which he considered to be a clinical entity and to which he gave the name *agranulocytic angina*. Rosenthal points out that the first case of this symptom-complex was described in 1902 by Brown. Schwartz reported a case in 1904 and a third case was described in 1907 by Türk. It was not until Schultz reported 6 cases, however, that general interest was aroused. Since 1922 a number of cases, more than 100, have been reported. A description of this syndrome, as modified by the observations of Friedmann, Kastlin, Ordway and Gorham, Rosenthal, and others, follows:

Symptomatology.—The patients have usually been women of middle age who frequently give no history of earlier predisposing ill health. A small proportion of cases has been reported in men and a few cases in children and in elderly individuals have been observed. The onset is sudden, with high fever, chills, general malaise, muscle pains, headache and marked prostration. Sore mouth, sore throat or difficulty in swallowing usually appear shortly after the onset of the illness. The patient looks very ill, although her mentality is quite clear until just before death. Pallor is characteristically absent. Slight jaundice has been observed in about 50 per cent of the cases. Purpuric and hemorrhagic manifestations are rare.

Extreme gangrenous stomatitis soon appears in the severe cases and develops very rapidly. In addition, ulceration may be found in other portions of the alimentary tract, on the anus, genitals or skin. The lesions are characteristically nonmarginated and there is very little or no reaction in the neighboring tissue. A membrane may cover the ulcerated area. Fusiform bacilli and spirochetes have been found in some cases. There may be slight regional adenopathy. The liver and spleen may or may not be enlarged.

* "Agranulocyte" is defined in the American Medical Dictionary as "a nongranular leukocyte."

CLINICAL COURSE.—The course of the disease in the cases described by Schultz was rapid and all of his patients died. The duration of the disease has been usually 4 to 10 days, but more acute as well as more protracted cases have been reported (2 to 90 days). Moore and Wieder, and Roberts and Kracke described cases in which recovery took place only to be followed by death in a second attack. Only about 10 per cent of the cases described by other observers since Schultz's report appeared have recovered, death usually occurring as the result of bronchopneumonia. The published mortality figures, however, are misleading, for undoubtedly many cases have occurred in which the symptoms are not as severe as suggested in the description of a typical case here presented. These cases are not reported but they have the ulcerative lesions of the buccal mucous membranes and the typical blood picture, and some of these patients recover without subsequent disability. We have observed such a case.

LABORATORY FINDINGS.—The blood findings are characteristic. Leukopenia is marked and there may be as few as 100 white corpuscles per c.mm. Granulocytes are very greatly reduced or entirely absent (4 to 0 per cent). Lymphocytes are relatively increased (60 to 100 per cent), but absolutely reduced. Values for monocytes have ranged from 0 to 18 per cent.

Reduction in the number of red corpuscles or in the quantity of hemoglobin was absent in the cases described by Schultz, but in some instances, in the later cases, slight or moderate anemia has been observed. Normal numbers of blood platelets are found.

Blood cultures were negative in 4 of Schultz's cases and the other two revealed the presence of pneumococcus and *Pneumococcus mucosus* respectively. In some of the later cases a large variety of organisms has been found in the blood, including staphylococcus, *Streptococcus haemolyticus* and *Bacillus coli*.

Diagnosis.—Further observation is necessary to establish the position of the syndrome described by Schultz. In all cases presenting such a picture, a source of infection should be sought and, if found, appropriately treated. Leon differentiates what he calls "symptomatic agranulocytosis" which results from a known infection, by the finding of a positive blood culture, reduction in both red corpuscles and platelets, the presence of a hemorrhagic tendency, the absence of jaundice and the discovery of septic splenitis at autopsy. In other instances a carefully taken history may reveal exposure to some poison such as benzol or radium.

Aplastic anemia is differentiated by the youth of the patient, the marked pallor, the presence of hemorrhages, the subacute course and the absence of any evidence whatever of bone marrow activity. Acute leukemia in a leukopenic stage may cause much confusion, but again the marked hemorrhagic tendency, the changes in the red corpuscles and the presence in large numbers of myelocytes and myeloblasts or young lymphocytes and lymphoblasts are differentiating features. Acute benign lymphadenosis (infectious mononucleosis) may present a slight resemblance to granulocytopenic angina, but the more benign course and the increased number of white corpuscles distinguish this condition from the syndrome of Schultz.

Treatment.—Treatment has been of no avail in many instances. In the recovered patients treatment has been supportive and in no sense specific. Friedemann and Elkeles have recently reported favorable results following the use of very small doses of roentgen irradiation of the bone marrow.

Pathology.—The outstanding feature revealed by autopsy is a lack of granulocytes. The erythropoietic tissue of the bone marrow is normal and megakaryocytes are found in normal numbers, but the granulopoietic tissue is aplastic and lymphocytes are prominent by contrast. The necrotic lesions in the mouth and other areas are sharply defined and polymorphonuclear leukocytes are conspicuously absent, only plasma cells and lymphocytes being found. The adjoining vessels show hyaline and fibrinous thrombi. Bronchopneumonia with a similar lack of granulocytes on histologic examination is commonly found. The liver is often enlarged and there may be evidence of necrosis. The spleen is frequently large and marked proliferation of the endothelial cells has been commonly noted (Rose and Houser).

Etiology.—This subject has been fully discussed by Rose and Houser and by Blumer. The separation of this syndrome as a specific disease entity has been seriously questioned. It may well be asked whether granulocytopenic angina represents a primary disease of the granulopoietic apparatus with secondary necrotic foci, or the reaction to an overwhelming septicemia in a subject with low resistance. Ordway and Gorham cite 3 cases in which blood changes were noted before changes in the tissues appeared. Roberts and Kracke found that blood changes occurred in their patient before any symptoms appeared. Rutledge, Hansen-Pruss and Thayer report a patient who suffers from cyclic attacks of granulocytopenia. The cause of the bone marrow paralysis in these cases can only be surmised and the activity of some potent toxin suspected. Blumer points out that the cases of agranulocytic angina cannot represent an inborn permanent reaction on the part of the individual as some patients have recovered and reacted normally to subsequent infections. Most observers feel that granulocytopenic angina is a nonspecific reaction to an infection of unusual virulence and that a variety of infecting organisms may cause it. Musser has discussed the reaction of the leukopoietic system to various types of throat infection and has shown that these reactions may vary from the ordinary hyperleukocytosis with polymorphonuclear increase to the type found in Schultz's disease. The occurrence of granulocytopenia with leukopenia in association with a large variety of poisonous and septic causes, already mentioned, may also be cited as an example of the nonspecificity of this condition.

BIBLIOGRAPHY

Leukemias

- AUBERTIN, C.: Origine myelogene de la leucemie aiguë, *Semaine méd.*, 24: 277-279, 1905.
 BAKER, L. F.: Neutrophilic myelocytes in the cerebrospinal fluid of a patient suffering from myeloid leukemia and their significance for the diagnosis of myeloleukemic infiltration of the leptomeninges, *South. M. J.*, 14: 437-442, 1921.
 BECLERE, A. AND BECLERE, H.: La radiotherapie dans les leucemies, *Tr. Internat. Cong. Med. Section 22, 1913, Radiology, Part 2*, 3-9, 1914.
 BENNETT, J. H.: Case of hypertrophy of spleen and liver in which death took place from suppuration of blood, *Edinburgh M. & S. J.*, 64: 413-423, 1845.
 RILLINGS, F.: Benzol in the treatment of leukemia, *J. Am. M. Ass.*, 60: 495-498, 1913.
 BOGGS, T. R. AND GUTHRIE, C. G.: Bence-Jones proteinuria in leukemia; report of 4 cases, *Bull. Johns Hopkins Hosp.*, 24: 368-372, 1913.
 BOIKAN, W. S.: Leukemic changes of the gastro-intestinal tract, *Arch. Int. Med.*, 47: 42-57, 1931.
 BOGESON, E. J. AND WAGENER, H. P.: Changes in eye in leukemia, *Am. J. M. Sc.*, 177: 668-676, 1929.
 BRANNAN, D.: Chloroma: the recent literature and a case report, *Bull. Johns Hopkins Hosp.*, 38: 189-216, 1926.
 CRAVER, L. F.: Tenderness of the sternum in leukemia, *Am. J. M. Sc.*, 174: 799-801, 1927.
 CRAWFORD, B. L. AND WEISS, E.: A consideration of leukemia, with especial reference to a subacute form, *Am. J. M. Sc.*, 175: 622-630, 1928.
 DAMESHEK, W.: Acute monocytic (histiocytic) leukemia, *Arch. Int. Med.*, 46: 718, 1930.
 EBSTEIN, W.: Ueber die akute Leukaemie und Pseudoleukaemie, *Deutsches Archiv. fur klin. Med.*, 44: 343-396, 1888-89.
 EHRLICH, P.: *Farbenanalytische Untersuchungen zur Histologie und Klinik des Blutes*, Berlin, A. Hirschwald, 1891.
 FRAENKEL, A.: Ueber akute Leukaemie, *Deutsche med. Wchnschr.*, 21: 639, 1895.
 FRIED, B. M.: Leukemia and the central nervous system, with a review of thirty cases from the literature, *Arch. Path. & Lab. Med.*, 2: 23-40, 1926.
 VON FRIEDREICH, N.: Ein neuer Fall von Leukaemie, *Virchows Arch. f. path. Anat.*, 12: 87-58, 1857.
 GULLAND, G. L. AND GOODALL, A.: *The Blood: A Guide to Its Examination and to the Diagnosis and Treatment of Its Disease*, Ed. 3, Edinburgh, W. Green & Son, Ltd., 1925.
 ISAACS, R.: Blood changes in the leucemias and the lymphomata and their bearing on roentgen therapy, *Am. J. Roent. and Rad. Ther.*, 24: 648-656, 1930.
 KETRON, L. W. AND GAY, L. N.: Myeloid leukemia of the skin, *Arch. Dermatol. and Syph.*, 7: 176-194, 1923.
 KRANTZ, C. I. AND RIDDLE, M. C.: The basal metabolism in chronic lymphatic leukemia, *Am. J. M. Sc.*, 175: 229-242, 1928.
 KRUMBHAAR, E. B.: Leukemoid blood pictures in various clinical conditions, *Am. J. M. Sc.*, 172: 519-533, 1926.
 MCALPIN, K. R. AND SANGER, B. J.: Blood counts and basal metabolism of leukemias under roentgen ray treatment, *Am. J. M. Sc.*, 167: 29-38, 1924.
 MINOT, G. R. AND BUCKMAN, T. E.: Blood platelets in the leukemias, *Am. J. M. Sc.*, 169: 447-485, 1925.
 NEUMANN, E.: Ein Fall von Leukaemie mit Erkrankung des Knochenmarkes, *Arch. d. Heilk. Leipzig*, 11: 1-14, 1870.
 ORDWAY, T.: Remissions in leukemia produced by radium in cases completely resistant to x-ray and benzol treatment, *Tr. Ass. Am. Physicians*, 31: 177-207, 1916.
 — AND GORHAM, L. W.: *The Diagnosis and Treatment of Diseases of the Blood*, Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 9: 1930.
 PINEY, A.: *Recent Advances in Haematology*, Ed. 2, London, J. & A. Churchill, 1928.

- RESCHAD, H. AND SCHILLING-TORGAU, V.: Ueber eine neue Leukaemie durch echte Uebergangsformen (Splenocytenleukaemia) und ihre Bedeutung fuer die Selbststaendigkeit dieser Zellen, München, med. Wchnschr., 60: 1981-1984, 1913.
- RIDDLE, M. C. AND STURGIS, C. C.: Basal metabolism in chronic myelogenous leukemia, Arch. Int. Med., 39: 255-274, 1927.
- ROSENKRANZ, G.: Hirnblutungen bei Leukaemie, Frankfurt. Ztschr. f. Path., 35: 359-373, 1927.
- ROWE, S. M.: Mikulicz's syndrome with chronic lymphatic leukemia, New England J. Med., 202: 863-865, 1930.
- ROWNTREE, L. G., BROWN, G. E. AND ROTH, G. M.: The Volume of Blood and Plasma in Health and Disease, Mayo Clinic Monographs, Philadelphia and London, W. B. Saunders Co., 1929.
- VIRCHOW, R.: Weisses Blut und Milztumoren, Med. Zeitung, 15: 157; 163, 1846.
- WARD, G. R.: Infective theory of acute leukemia, Brit. J. Child. Dis., 14: 10-20, 1917.
- WARREN, S. L.: Acute leukemia: review of literature and 28 new cases, Am. J. M. Sc., 178: 490-500, 1929.

Acute Benign Lymphadenosis (Infectious Mononucleosis)

- BLOEDORN, W. A. AND HOUGHTON, J. E.: The occurrence of abnormal leukocytes in the blood in acute infections (acute benign lymphoblastosis), Arch. Int. Med., 27: 315-325, 1921.
- CABOT, R. C.: The lymphocytosis of infection, Am. J. M. Sc., 145: 335-339, 1913.
- CADY, L. D.: The diagnosis of sporadic infectious mononucleosis (glandular fever), Am. J. M. Sc., 175: 527-542, 1928.
- CLOUGH, PAUL W.: Diseases of the Blood, New York and London, Harper & Brothers, 1929.
- DOWNEY, H. AND MCKINLAY, C. A.: Acute lymphadenosis compared with acute lymphatic leukemia, Arch. Int. Med., 82: 82-112, 1923.
- FOX, H.: Infectious mononucleosis: histology of tonsil and lymph node, Am. J. M. Sc., 173: 486-489, 1927.
- GILBERT, R. AND COLEMAN, M. B.: Laboratory findings in an epidemic of glandular fever, Am. J. Hyg., 5: 35-48, 1925.
- GORHAM, L. W., SMITH, D. T. AND HUNT, H. D.: The experimental reproduction of the blood picture of infectious mononucleosis in the guinea pig. Proceedings of the Twenty-first Annual Meeting of the American Society for Clinical Investigation, Atlantic City, N. J., 1929, J. Clin. Investigation, 7: 504, 1929.
- GUTHRIE, C. C. AND FESSEL, J. F.: An epidemic of glandular fever in a preparatory school for boys, Am. J. Dis. Child., 29: 492-496, 1925.
- LONGCOPE, W. T.: Infectious mononucleosis (glandular fever), with report of ten cases, Am. J. M. Sc., 164: 781-808, 1922.
- LÜDKE, H.: Ueber die experimentelle Erzeugung leukämieähnlicher Blutbilder, Deutsches Archiv. f. klin. Med., 100: 552, 1910.
- MARCHAND, F.: Ueber ungewöhnlich starke Lymphocytose im Anschluss an Infektionen, Deutsches Arch. f. klin. Med., 110: 359-372, 1913.
- PFEIFFER, E.: Drüseneieber, Jahrb. f. Kinderh., 29: 257-164, 1889.
- SPRUNT, T. P. AND EVANS, F. A.: Mononuclear leukocytosis in reaction to acute infections ("infectious mononucleosis"), Bull. John Hopkins Hosp., 31: 410-417, 1920.
- TIDY, H. L. AND DANIEL, E. C.: Glandular fever and infective mononucleosis; with account of an epidemic, Lancet, 2: 9-13, 1923.
- TÜRK, W.: Septische Erkrankungen bei Verkümmern des Granulocytensystems, Wien. klin. Wchnschr., 20: 157-162, 1907.

Granulocytopenia

- BLUMER, G.: The agranulocytic blood picture in conditions other than angina, Am. J. M. Sc., 179: 11-16, 1930.
- BROWN, P. K. AND OPHULS, W.: A fatal case of acute primary infectious pharyngitis with extreme leukopenia, Am. Med., 8: 649-651, 1902.
- DOAN, C. A., ZEPFAS, L. G., WARREN, S. AND AMES, O.: A study of the mechanism of nucleinate induced leucopenic and leucocytic states, with special reference to the relative roles of liver, spleen and bone marrow, J. Exper. Med., 57: 403, 1928.
- FARMAKIDIS, C.: De quelques cas d'agranulocytose au cours de la diphtérie, Presse méd., 37: 1121-1123, 1929.
- FRIEDEMANN, U.: Angina agranulocytotica, Ztschr. f. klin. Med., 108: 54-66, 1928.
- AND ELKELES, A.: Roentgen treatment of agranulocytosis, Deutsch. med. Wchnschr., 56: 947, 1930.
- KASTLIN, G. J.: Agranulocytic angina, Am. J. M. Sc., 173: 799-813, 1927.
- LEON, A.: Ueber grangränzender Prozesse mid Defekt des Granulocytensystems ("Agranulocytosen"), Deutsches Arch. f. klin. Med., 143: 118-128, 1923.
- MOORE, J. A. AND WIEDER, H. S.: Agranulocytic angina, J. Am. M. Ass., 85: 512-513, 1925.
- MUSSEY, J. H.: The leukocytic response to throat infections, M. Clin. N. Amer., 12: 1377-1389, 1929.
- ORDWAY, T. AND GORHAM, L. W.: In Oxford Monographs on Diagnosis and Treatment, New York, Oxford University Press, 9: 204, 1930.
- REZNIKOFF, P.: Experimental leukocytosis and leukopenia, J. Clin. Investigation, 6: 16, 1928.
- : Nucleotide therapy in agranulocytosis, J. Clin. Investigation, 9: 381-391, 1930.
- ROBERTS, S. R. AND KRACKE, R. R.: Agranulocytosis, J. Am. M. Ass., 95: 780, 1930.
- ROSE, E. AND HOUSER, K. M.: Identity of so-called agranulocytic angina; report of case, Arch. Int. Med., 43: 533-548, 1929.
- ROSENTHAL, NATHAN: Hematological aspects of agranulocytosis and other diseases accompanied by extreme leukopenia, Am. J. Clin. Path., 1: 7, 1931.
- : Observations on agranulocytosis, New York State J. Med., 30: 695-699, 1930.
- RUTLEDGE, B. H., HANSEN-PRUSS, O. C. AND THAYER, W. S.: Recurrent agranulocytosis, Bull. Johns Hopkins Hosp., 46: 869, 1930.
- SCHULTZ, W.: Ueber eigenartige Halserkrankungen (a) Monocyten Angina, (b) Gran-gränzender Prozesse und Defekt des Granulocytensystems, Deutsche med. Wchnschr., 48: 1495, 1922.
- SCHWARTZ, E.: Ein Fall von extremer Leukopenia, Mitt. d. Gesellsch. f. inn. Med. u. Kinderh., 8: 190, 1904.
- TÜRK, W.: Septische Erkrankungen bei Verkümmern des Granulocytensystems, Wien. klin. Wchnschr., 20: 157-162, 1907.

CHAPTER V

DISEASES ASSOCIATED CHIEFLY WITH ALTERATIONS IN THE PLATELETS AND THE MECHANISM OF BLOOD COAGULATION

By JOHN H. MUSSEY, M.D., AND MAXWELL M. WINTROBE, M.D.

PURPURA, p. 883—Definition, p. 883—Classification, p. 883.

ESSENTIAL THROMBOCYTOPENIC PURPURA, p. 884—Synonyms, p. 884—Definition, p. 885—Etiology, p. 885—Symptomatology, p. 885—Blood changes, p. 886—Clinical course, p. 886—Diagnosis, p. 886—Treatment, p. 887.

ANAPHYLACTOID PURPURA, p. 888—Definition, p. 888—Etiology, p. 888—Symptomatology, p. 888—Laboratory findings, p. 889—Diagnosis, p. 889—Treatment, p. 889—Prognosis, p. 889.

OTHER FORMS OF PRIMARY NONTHROMBOCYTOPENIC PURPURA, p. 890—Purpura simplex, p. 890—Purpura fulminans, p. 890—Purpura senilis, p. 890—Purpura cachectica, p. 890—Mechanical purpura, p. 890—Familial and hereditary purpura, p. 890.

HEMOPHILIA, p. 890—Synonyms, p. 890—Definition, p. 890—Etiology, p. 890—Symptomatology, p. 891—Blood changes, p. 892—Diagnosis, p. 892—Treatment, p. 893—Prognosis, p. 894—Pathology, p. 894.

HEMORRHAGIC DISEASE OF THE NEWLY-BORN, p. 894—Synonyms, p. 894—Definition, p. 894—Etiology, p. 894—Symptomatology, p. 894—Laboratory findings, p. 894—Diagnosis, p. 895—Treatment, p. 895—Prognosis, p. 895—Pathology, p. 895.

PURPURA

Definition.—Although strictly speaking the term "purpura" refers to the color of certain skin lesions, it is now generally employed to refer to a symptom-complex which is characterized by subcutaneous or submucous hemorrhage, bleeding from mucous membranes and, much more rarely, into serous cavities. The subcutaneous hemorrhages may be minute (petechiae) or very extensive (ecchymoses). Furthermore, the skin lesions included under this heading not only may consist of purple hemorrhagic areas but also may take the form of various types of erythema.

Classification.—The symptom purpura may be one of the accompanying manifestations of a large variety of infectious and other diseases of known causation, it may be associated with some of the so-called "diseases of the blood," already described, it may follow poisoning by various substances or it may be the chief symptom of several diseases of unknown etiology, the essential or primary purpuras. The latter types are so called because of a total lack of knowledge concerning their causation and the name "primary" or "essential" implies that they originate in some disorder of the mechanism by which blood is held within the capillary bed and large blood vessels. Purpura that is associated with infections or intoxications of known causation, or with one of the blood diseases, is spoken of as being secondary.

One of the most striking phenomena which has been observed in certain forms of purpura is a reduction in the number of platelets in the blood. The purpuras have therefore been classed as thrombopenic and nonthrombopenic. Such a subdivision is useful for many reasons but unfortunately the same factor, as, for example, infection, may at one time be associated with thrombocytopenia, whereas at other times a normal number of blood platelets is found. Such variations suggest that factors other than the number of circulating blood platelets are important in the occurrence of purpura, and until the entire mechanism of the production of this symptom is better understood an entirely satisfactory classification cannot be expected. It may well be borne in mind that while the purpuras in general frequently show variations from the normal in the blood findings, and hence are classified under the term "blood dyscrasias," it is impossible to have the characteristic symptom of minute or large hemorrhage without injury to the endothelium of the capillaries or large blood vessels.

Bearing these reservations in mind, the following classification, adapted from Leschke, and from Pratt, may be employed:

I. Thrombocytopenic Purpura.

1. Essential or Primary (Werlhof's Disease).

2. Symptomatic or Secondary.

- a. In blood diseases (aplastic anemia, leukemia, pernicious anemia).
- b. Infections (sepsis, subacute bacterial endocarditis, typhoid, tuberculosis, etc.).
- c. Intoxications (benzol, arsphenamine, snake venom, etc.).
- d. Radiation (x-ray, radium, etc.).
- e. Diseases associated with splenomegaly (hemolytic icterus, Gaucher's disease, etc.).
- f. Tumors, metastases, sclerosis of bone marrow.
- g. Anaphylaxis.
- h. Avitaminosis.

II. Nonthrombopenic Purpura.

1. Essential or Primary.

- a. Anaphylactoid purpura (purpuras of Schönlein and Henoch and erythemas of Osler).
- b. Miscellaneous group (purpura simplex, purpura fulminans, purpura senilis, purpura cachectica, mechanical purpura, familial and hereditary purpura).

2. Symptomatic or Secondary.

- a. Various chronic diseases (chronic nephritis, cardiac disease, etc.).
- b. Infections (scarlet fever, typhoid, etc.).
- c. Intoxications (benzol, arsphenamine, iodine, snake venom, etc.).
- d. Avitaminosis (scurvy).

For the differentiation of these various types of purpura, there are necessary not only a full history, physical examination and the usual study of the blood, but, in addition, (1) an accurate platelet count, (2) bleeding time, (3) coagulation time, (4) retractivity of the blood clot. The technic of these tests has already been discussed in Chapter II, this section. And (5) the capillary resistance or *tourniquet test*, which is best carried out by placing the cuff of the blood pressure apparatus on the arm of the patient, setting the pressure midway between the systolic and diastolic level, and maintaining such pressure for 5 or 10 minutes. When the test is positive a variable number of petechial spots or ecchymoses will appear scattered diffusely over the forearm distal to the tourniquet. This is also known as the Rumpel-Leede phenomenon and was originally employed in the diagnosis of scarlet fever. Purpura may also be produced in certain cases by striking the skin over the sternum or tibia with a rubber-tipped percussion hammer or by injecting subcutaneously 1 to 2 c.c. of saline solution (Hess). These capillary resistance tests simply demonstrate the vulnerability of the capillaries and are not limited in their occurrence to the purpuras.

In the thrombopenic purpuras bleeding time is prolonged and the clot is non-retractile but coagulation time is normal. In the nonthrombopenic purpuras the blood is usually quite normal in all these respects. The capillary resistance test is positive in the first group and may or may not be positive in the second.

Only the primary purpuras will be described here. The secondary forms will be discussed under Differential Diagnosis.

ESSENTIAL THROMBOCYTOPENIC PURPURA

(Primary, Idiopathic)

Synonyms.—Purpura haemorrhagica, essential thrombopenic purpura (Frank), Werlhof's disease, morbus maculosus werlhofii, thrombocytolytic purpura (Kaznelson), purpura thrombopenica (Schultz), hemogenia (Weil), hemogenic syndrome (Roskam).

Definition.—Essential thrombocytopenic purpura is a condition of unknown etiology characterized by petechiae or ecchymoses in the skin, hemorrhage from mucous membranes, a reduced platelet count, prolonged bleeding time, non-retractile clot and normal coagulation time. The skin lesions are not associated with erythema, swelling or inflammation.

Etiology.—This condition occurs most frequently in children and young adults. Hereditary and familial examples of the disease have been described by Leschke and Wittkower, by Liebling and by Hess but these are rare. The onset of essential thrombocytopenic purpura has in some instances been preceded by acute or chronic infections. Its causation is unknown and the nature of the physiologic disturbance remains a mystery. The most thought-provoking phenomena noted in connection with this disease are the marked reduction in the number of blood platelets and the striking improvement which follows splenectomy, an improvement which takes place even in the presence of a platelet count as low as before the operation.

A number of theories have been offered in explanation of the changes observed in this condition, but there is really very little convincing evidence to support them. It has been proposed that the megakaryocytes of the bone marrow, which are now generally believed to be the parent cells of blood platelets, are abnormal in some way. Seeliger found these giant cells in normal or excessive numbers in the bone marrow of patients suffering from essential thrombocytopenia, but the granulation which is normally found in the cytoplasm of these cells was absent. Frank believes that the spleen exerts an inhibitory influence on the formation of platelets. Kaznelson suggests that the platelets are destroyed by the spleen more rapidly than is normal. Others view as a possibility the presence of some abnormality in the functioning of the reticulo-endothelial system as a whole. The work of Aschoff and of Krogh indicates that the permeability of the capillaries may depend on variations in the functional integrity of the reticulo-endothelial cells. Bedson's experiments suggest that abnormal capillary permeability to blood may be the initial disorder in purpura and that the platelets are used up in an attempt to defend the weakened areas. When the capillary damage is widespread all of the platelets may be used up without supplying adequate protection and therefore hemorrhage results. The fact that thrombocytopenic purpura may be produced by poisons and is sometimes associated with infection calls to mind the possibility that the exciting agent in such capillary damage may be some undiscovered infectious agent or toxin.

Symptomatology.—Acute and chronic forms of this illness are encountered, the latter being about nine times as common as the former. Chronic thrombocytopenic purpura may be intermittent or continuous in its course. The onset is frequently abrupt and is manifested by uncontrollable epistaxis or by hemorrhage after tooth extraction or tonsillectomy, prolonged menstruation, purpuric and ecchymotic eruptions, hematuria, melena or conjunctival and even cerebral hemorrhage. Visceral or joint hemorrhages are rare. Other symptoms depend on the location of the hemorrhage and its severity. Fever occurs only secondarily to infection complicating hemorrhage. One of our patients, a girl of 7 years, appeared with purpuric eruptions and nosebleed. The same symptoms had first appeared two months before but had cleared up in a week. Ever since birth the slightest trauma had produced "blue spots." Another patient, a girl of 15 years, complained of weakness, epistaxis and vaginal bleeding which had been continuing for 46 days. Before puberty she had suffered from vaginal bleeding on two occasions.

The patient may look well or may appear pale and present other evidences of anemia, these features depending on the severity and duration of the blood loss. The skin lesions vary greatly in size, may be bright or deep red, purplish or any of the colors which are commonly formed in a "black and blue spot." These areas are irregular in distribution, rarely symmetrical and not swollen or erythematous unless there has been secondary infection. Intramuscular hematomata may be somewhat tender. Soft blood clots may be found in the nose or

mouth. Less commonly there may be physical signs of hemorrhage into the brain, spinal cord or elsewhere. There is no evidence of urticaria. The spleen is usually not palpable.

BLOOD CHANGES.—The changes in red cells and hemoglobin depend on the amount of blood lost. Any of the findings already described in the discussion of posthemorrhagic anemia may be encountered. Slight leukocytosis may be found or the white cells may be normal in number. Platelets are markedly reduced in number in the active stages of the disease and may remain below normal even when hemorrhage is not occurring. Bleeding usually commences when the platelets are reduced to 60,000 per c.mm. or less. Counts below 1,000 per c.mm. have been recorded. The platelets in the blood smear may appear very small or excessively large and usually stain very deeply.

Bleeding time is greatly prolonged as a rule and oozing may continue for several hours. The blood clot jels at the usual time but does not retract, remaining soft and jelly-like even after it has been detached from the sides of the test tube. Coagulation time is normal. The capillary resistance test is positive. In carrying out these tests the details of technic already outlined should be carefully followed and to be of value they should be performed more than once.

CLINICAL COURSE.—In acute cases the duration of the disease may be a few days or a few weeks. Death may follow, spontaneous recovery may occur, or the disease may become chronic. Chronic cases are more common and such patients may live for many years. Acute exacerbations frequently occur. Blood findings may or may not be normal between attacks.

Diagnosis.—The blood examinations necessary for the study of any patient presenting symptoms of prolonged bleeding, purpuric eruptions or similar manifestations have already been discussed (p. 884). Should thrombocytopenia be encountered these blood studies as well as a thorough physical examination and a history in the taking of which the possible presence of hereditary or familial hemorrhagic tendencies and the possibility of occupational disease have been particularly borne in mind, will make it possible to discover or rule out some of the causes of **secondary thrombocytopenic purpura**.

(a) **BLOOD DISEASES.**—*Aplastic anemia* may clinically be mistaken for essential thrombopenic purpura but the marked reduction in the number of red and white corpuscles, as well as of platelets, and the marked relative lymphocytosis are important differentiating features. When anemia is marked in essential thrombocytopenic purpura, the red cells show the changes noted in posthemorrhagic anemia such as microcytosis, poikilocytosis and marked achromia. In aplastic anemia the red corpuscles are relatively normal in appearance.

Acute leukemia, especially at a time when leukocytosis is absent or slight, may be confused with essential thrombopenic purpura. It must be borne in mind that *in any condition associated with thrombocytopenia bleeding time is prolonged, the clot is non-retractile and the tourniquet test positive*. Differentiation in cases of acute leukemia in the aleukemic or subleukemic stage depends on the finding of numerous immature leukocytes. The latter do not occur in essential thrombocytopenic purpura. Clinically differentiation may be difficult but marked fever and prostration, severe ulcerative changes in the mouth and glandular enlargement suggest acute leukemia rather than essential thrombocytopenic purpura. *Chronic leukemia*, even in the "aleukemic" stage, should rarely cause any difficulty. Although platelets may be reduced in number the clinical features and the presence of immature leukocytes should leave no room for confusion.

Pernicious anemia in an aplastic stage, may be associated with purpura and thrombocytopenia but such characteristic clinical features as sore tongue, achlorhydria and neurologic changes and such blood findings as macrocytosis, megaloblasts and bilirubinemia should leave no ground for confusion.

Purpuric and hemorrhagic manifestations are very rare in *granulocytopenic* ("agranulocytic") *angina*. Marked or total absence of granulocytes is not encountered in essential thrombocytopenic purpura.

(b) **INFECTIONS.**—Purpura with thrombocytopenia is very occasionally encountered in infections such as typhoid fever, tuberculosis (especially the miliary form), smallpox, measles and subacute bacterial endocarditis. In the last condition anemia may be quite great and the resemblance to the disease under discussion may be marked (Pepper, Rosenthal). Careful examination usually, however, will readily rule out any of these infections.

(c) **INTOXICATIONS.**—Such substances as benzol, arsphenamine, aniline and quinine (Rosenthal) may poison the bone marrow in such a manner as to produce thrombocytopenia. Subsequently, leukopenia occurs and eventually the erythropoietic tissues may be affected with the production of an aplastic anemia.

(d) **DEEP RADIATION** by means of roentgen rays or radium and the ingestion, inhalation or injection of radio-active substances such as radium salts or solutions of thorium X are occasional causes of thrombopenia and purpura.

(e) **IN VARIOUS DISEASES ASSOCIATED WITH SPLENOMEGALY** such as hemolytic icterus, Gaucher's splenomegaly, splenic anemia and thrombosis of the splenic vein, purpuric manifestations may occur (Rosenthal). Marked splenomegaly in itself suggests that the case is not one of essential thrombocytopenic purpura.

(f) **BONE MARROW TUMORS, METASTASES AND OSTEOSCLEROSIS** may cause thrombocytopenia by crowding out of hemogenetic tissue. Roentgen ray examinations of the bones may thus be of value in determining the cause of obscure forms of thrombopenic purpura.

Very rarely thrombocytopenic purpura may occur (g) as part of an **ANAPHYLACTIC** reaction or (h) as the result of food deficiency (**AVITAMINOSIS**).

Treatment.—**Rest in bed** during the acute stages, **good nursing** with a view particularly to the prevention of skin injury and secondary infection, and an appetizing, well balanced diet are essential. There does not appear to be the specific benefit from liver diet in this condition such as is found in pernicious anemia, but it should be borne in mind that **liver and other substances**, which have been shown to be valuable in hemoglobin production, as well as large doses of iron, even though their use is not followed by spectacular results, are of value in the treatment of the posthemorrhagic anemia which is often a complication of thrombopenic purpura.

Drugs such as calcium lactate or calcium chloride and blood coagulants seem to be of no benefit in this condition. **Ultra-violet light** has been advocated (Sooy and Moise). Ordway and Gorham have found the **subcutaneous or intramuscular injection of whole unmatched blood**, 20 c.c. every day or every other day, of benefit. The favorable influence of such injections may depend on a foreign protein reaction. Gram reported favorable results following **milk injections**.

Blood transfusion is usually of value although the benefit is frequently only temporary. Whole blood is preferable because the use of citrate and the subsequent filtration of the blood removes at least some of the platelets from the transfused blood. Transfusions may be of value in stimulating the bone marrow and perhaps, by supplying blood platelets, may serve to tide the patient over for a time. To secure the latter effect **transfusions must be repeated every two or three days** as the life of the platelets is very brief. Transfusion is always a useful measure prior to operation. Rarely transfusion is followed by increased bleeding.

Splenectomy, first suggested as a form of treatment in this disease by Hess and successfully performed in 1916 by Kaznelson, is followed by amazing improvement in chronic forms of essential thrombopenic purpura. The data published by Whipple, by Spence and by others attest to this statement. Bleeding ceases, purpuric eruptions disappear, bleeding time and clot retractivity return to normal, and the tourniquet test becomes negative. There is not infrequently a platelet "crisis" following the operation with a rise in the platelet count to 500,000 or 1 million per c.mm. These soon again become reduced in number, but in spite of platelet counts which may be as low as before the operation, bleeding usually does not recur. The ultimate fate of these patients requires further study. Of 61 followed-up cases collected by Whipple, good results were found in 51. Six showed no improvement. Infection seems to play

a part in the production of a relapse. Morrison, Lederer and Fradkin suggest the presence of accessory spleens as the cause of relapse.

The first prerequisite when splenectomy is considered in essential thrombopenic purpura is **accurate diagnosis**. Splenectomy is valueless and usually distinctly contraindicated in the symptomatic forms of thrombopenic purpura. Greater discrimination in the selection of cases will probably be followed by more favorable therapeutic results. The **general condition of the patient** is another important consideration. **Splenectomy should be carried out in essential thrombopenic purpura whenever there is danger to life or to normal growth and development from the anemia resulting from blood loss.** Splenectomy should be performed **before the illness has progressed too far.** It is somewhat debatable whether the operation should be performed during an acute stage. The operative mortality in chronic cases has been about 10 per cent, but in the acute cases about 80 per cent have died. Some advise that in acute cases transfusions only be employed and a more favorable opportunity for operation awaited. Reuben and Claman, and Killin, however, advise early diagnosis and operation. Van Goidsenhoven suggests **ligation of the splenic artery** as offering less risk and equally good results.

Such measures as hysterectomy or oöphorectomy cannot be advocated for the treatment of excessive uterine bleeding in primary thrombopenic purpura as they are only palliative. If blood loss is sufficiently severe to necessitate operation, splenectomy should be performed.

ANAPHYLACTOID PURPURA

Definition.—Under this heading is included a large group of nonthrombopenic purpuras which includes Henoch's purpura, Schönlein's purpura (purpura rheumatica, peliosis rheumatica), and Osler's erythemas associated with visceral manifestations such as erythema simplex, erythema multiforme (bullosum, vesiculosum), erythema nodosum, urticaria pigmentosa, angioneurotic edema and similar conditions. These disorders are characterized by such symptoms as urticaria, edema, swollen joints, rheumatic pains, intestinal colic, hemorrhage from the bowel and very varied erythematous and purpuric skin lesions. As Christian points out, these anaphylactoid manifestations should perhaps be described as vasomotor disturbances, but they are still retained among the blood diseases because of their resemblance to purpuric conditions related more definitely to changes in the blood.

Etiology.—Osler pointed out that many of the symptoms and signs of these forms of purpura resemble those of serum sickness. The term "anaphylactoid" was proposed by Pfaundler and later by Frank. The latter has suggested that these conditions are produced by the histamine-like action of split-protein products absorbed into the body. It is known that histamine may cause dilatation of the capillaries with increased permeability. Ordway and Gorham cite a case in which an erythematous, blotchy eruption followed after the injection of antityphoid vaccine. Infection is cited as a cause of some of these conditions. It is true that they are often associated with tuberculosis. That some cases may represent examples of true food allergy is indicated by the observations of Alexander and Eyermann and of Kahn. Christian has suggested that various focal lesions may account for the location of the manifestations of these conditions in skin, viscera, joints or elsewhere.

Symptomatology.—The onset of the illness is frequently preceded by symptoms of infection and toxemia such as lassitude, headache, loss of appetite and fever. In peliosis rheumatica pain or tenderness about the joints, especially those at the ankles and knees, appears and may even precede any skin eruption. There may be diffuse ill-defined pains in the arms and legs and shifting of symptoms from joint to joint, thus suggesting rheumatic fever. In Henoch's type of purpura gastro-intestinal symptoms are most prominent. These include nausea, vomiting, diarrhea, constipation and colicky abdominal pain. The pain may be quite severe and may be located in the epigastrium, in the lower abdomen or about the umbilicus. Bile-stained and even blood-stained material may

be vomited. With the bowel movements mucus and blood may be passed. These symptoms may appear before any purpuric eruptions become evident and may thus lead to unnecessary and unfortunate surgical intervention as the patient may die of post-operative hemorrhage. Constipation in some instances has been so severe as to suggest intestinal obstruction.

In addition to these rheumatic and abdominal manifestations, hemorrhages from mucous membranes may occur and a large variety of skin eruptions usually appear. Not only are there subcutaneous and perhaps submucous hemorrhages but marked urticarial manifestations or even pemphigoid lesions may be prominent. There may be simple erythema which disappears on pressure or raised areas with wheals in the center as well as angioneurotic edema of the hands, eyelids and feet may be encountered. The skin lesions may be of all sizes and shapes. They are found most frequently in the extremities and are often symmetrically placed. They may appear in crops, and although itching is usually absent, various forms of paresthesia may be troublesome.

The actual joint involvement as a rule is not very severe, though the pain may be extreme prior to the oncoming of the cutaneous manifestations. Slight swelling and tenderness of the joints is usual. Localized or diffuse abdominal tenderness and even rigidity may be present.

LABORATORY FINDINGS.—*Blood.*—There is no anemia. Neutrophilic leukocytosis is common. Blood platelets are not significantly affected. Bleeding time, clot retractivity and coagulation time are normal. The tourniquet test may be positive or negative.

The *urine* may be normal, albuminuria may be noted, or actual acute nephritis may occur. Examination of the *stools* may reveal the presence of blood.

Diagnosis.—Before purpura appears real difficulty may be encountered in diagnosis. If fever and leukocytosis accompany the symptoms described, which not infrequently occurs, the clinical picture of some inflammatory process may be closely simulated. Skin manifestations should be carefully sought. When purpura is evident there is less difficulty. A platelet count serves to distinguish this form of purpura from the thrombopenic varieties. Other forms of primary nonthrombopenic purpura are usually readily differentiated.

Symptomatic nonthrombopenic purpura may be found in the following conditions:

(a) **CHRONIC DISEASES** such as heart disease or chronic nephritis with hypertension may rarely be associated with purpura. The platelets are usually normal in number although Rosenthal has reported 5 cases with thrombocytopenia. He found purpura in 4 cases of jaundice. In these cases platelets were normal but the tourniquet test was positive. It is possible that some alteration in the calcium factor takes place in such cases of jaundice associated with purpura.

(b) **INFECTIONS** such as subacute bacterial endocarditis, diphtheria, scarlet fever and typhoid fever may be associated with nonthrombopenic purpura.

(c) **INTOXICATIONS** produced by benzol, arsphenamine, phenacetin, salicylic acid, iodides, quinine, chloral hydrate, atropine, merbaphen (novasurol) and snake venom may be associated with purpura. It may be recalled that some of these substances also cause thrombocytopenia.

(d) **AVITAMINOSIS (Scurvy).**—In this disease the history of food deficiency and such characteristic symptoms as sponginess of the gums and subperiosteal hemorrhages are distinguishing features. Platelets are normal in number, clot retraction is normal and the tourniquet test may be either positive or negative.

Treatment.—Treatment of anaphylactoid purpura is unsatisfactory. Symptoms should be met as they arise and an attempt should be made to discover a cause. **Adrenaline**, 0.5 to 1 c.c. of a 1/1000 solution subcutaneously, may be very effective when urticarial manifestations are present. **Skin tests** should be carried out and **manifestations of allergy** sought. These if found should be appropriately treated. There is much doubt about the value of calcium salts in the treatment of these forms of purpura.

Prognosis.—This is uncertain. The condition may last a few days, or a few weeks. Recurrence is common. This form of purpura is rarely fatal unless

some complication such as tuberculosis, acute nephritis or cerebral hemorrhage supervenes.

OTHER FORMS OF PRIMARY NONTHROMBOPENIC PURPURA

Purpura Simplex.—These are mild cases which arise without any apparent cause and present purpuric skin manifestations which are not associated with any constitutional symptoms.

Purpura Fulminans.—This is a rare form of purpura which develops suddenly and runs a rapidly fatal course of 1 or 2 days. Fever and purpuric manifestations are the only striking indications of the nature of the ailment. This malady occurs chiefly in children.

Purpura Senilis and Purpura Cachectica.—These are names given to the extravasations of blood occasionally observed in old or ill-nourished individuals when no better cause can be named than capillary weakness.

Mechanical Purpura.—Constriction of a limb by means of a tourniquet, violent muscular contractions such as occur in epileptic seizures and whooping-cough and trauma may cause rupture of capillaries with consequent extravasation of blood into the tissues. The purpura observed in association with edema in the lower limbs in cases of heart disease is of similar mechanical origin.

Familial and Hereditary Purpura (Hereditary Hemorrhagic Thrombasthenia, Glanzmann).—This is a form of purpura of hereditary and familial occurrence. Both sexes are affected. Transmission has usually been through the female in the cases reported. The reader is referred to the article by Christian for a discussion of these and other rare forms of purpura.

HEMOPHILIA

Synonyms.—Hemorrhagic diathesis, hematophilia, Bluterkrankheit, hemophil.

Definition.—Hemophilia is a constitutional anomaly which depends on the hereditary transmission of a sex-linked recessive mendelian characteristic and is characterized by a lifelong tendency to prolonged hemorrhage and a markedly delayed coagulation time.

Etiology.—That a tendency to prolonged and even fatal hemorrhage may be familial has long been recognized, as is evident from the writings of Rabbi Simon ben Gamaliel (second century A.D.) in the Talmud. Such an anomaly is mentioned in the writings of Maimonides, a physician and one of the greatest of Jewish philosophers, and in those of Albucasis, the Arab (twelfth century). The hereditary tendencies of hemophilia have been the subject of exhaustive studies by geneticists, among which may be mentioned those of Nasse, of Legg and of Bulloch and Fildes. The recent papers published by Lloyd and by Macklin summarize our knowledge concerning this aspect of the condition.

Hemophilia is a "constitutional anomaly" (Pratt) dominant in the male and recessive in the female. An affected male, provided he marries a normal woman, does not transmit the anomaly directly but each of his daughters, outwardly normal, is capable of transmitting the trait as an evident defect to half her sons and as a recessive or hidden characteristic to half her daughters. The sons of an affected male will not only be normal themselves, but they cannot transmit the defect to any of their descendants. Theoretically it is possible for a woman to show hemophilia but it is necessary that her father manifest the abnormality and that her mother be a carrier or a hemophiliac herself. An unequivocal case of hemophilia in a female has not been recorded. This is not surprising in view of the nature of the union required. Macklin suggests, furthermore, that the presence of a double quantity of the defect may act as a lethal factor which inhibits the development of the embryo.

The nature of the physiologic disturbance on which this tendency to prolonged bleeding depends is not fully understood. The discovery by Wright in 1893 that hemophilic blood exhibits a delayed coagulation time gave the impetus to numerous studies concerning this function of the blood. Among these may be mentioned the investigations of Addis, of Howell and of Minot and Lee. It

appears that prothrombin, antithrombin, calcium salts, thrombin and fibrinogen are all present in hemophilic blood in normal amounts. Platelets are not reduced in number. Bleeding time is usually normal and a firm, retractile clot is eventually formed. Of great significance are the experiments of Minot and Lee who added platelets of hemophilic blood to normal plasma and found a delayed clotting time as compared with that of samples in which normal platelets were added to normal plasma or to hemophilic plasma. This, they felt, indicated that the platelets are qualitatively defective in hemophilia. Howell and Cekada have recently shown that before coagulation takes place the blood platelets agglutinate and disintegrate, yielding thus a thromboplastic substance. It appears, then, that in hemophilia, through increased resistance of the blood platelets to disintegration, thromboplastin is liberated more slowly than is normal with the result that the entire process of coagulation is delayed.

Thromboplastic substance is derived from the tissues as well as from blood platelets. Gressot has shown that this substance is readily yielded by the tissue juice of hemophiliacs. A question of great moment which logically arises is concerned with the slow coagulation of hemophilic blood even though the wound is irregular rather than cleancut and when presumably much tissue juice is liberated. Addis explains this by pointing out that when a wound is made blood escapes and fills the cavity. At the periphery of the cavity thromboplastin from the injured tissues mixes with the blood and a firm fibrin layer is formed. This layer prevents tissue element from reaching the blood which flows from the injured vessels. Since the escaping blood is thus made to depend upon liberation of thromboplastin from the platelets, a process which is very slow in hemophilia, there is no wonder that an imperfect clot is formed and oozing of blood continues. Several observers have pointed out that if all the blood clot is carefully removed from a contused wound in a hemophiliac and cotton-wool soaked in normal blood applied to the entire wounded area, bleeding will cease.

Symptomatology.—The friction of a toothbrush on the gums, a slight cut, biting the tongue, the extraction of a tooth, circumcision or tonsillectomy may initiate prolonged and even fatal bleeding in an individual who manifests this constitutional anomaly. Epistaxis is a frequent complaint. Hemorrhage into subcutaneous tissue, muscles and particularly into joints may arise as the result of the slightest injury or sometimes apparently spontaneously. Internal hemorrhages are unusual but hematuria, melena and even hematomyelia have been recorded.

The bleeding is of the nature of persistent slow oozing. This tendency to prolonged bleeding presents itself almost invariably in early childhood, often in the first year of life, although hemorrhage from the umbilical cord is unusual. Probably the blood platelets of the mother protect the infant for the first 2 or 3 days of life. A remarkable feature of the bleeding is its variability. Hemorrhage may be slight at one time and alarmingly prolonged on some other occasion. Hematomata form readily but purpuric skin blotches are very unusual.

Very commonly joint symptoms are presented by hemophiliacs. Hemorrhage occurs into the joint cavity or into the diaphysis or epiphysis of the bone. Usually one joint is involved at any one time, although eventually many joints may suffer. The knee is the commonest site of such hemorrhage, but any joint may be involved. The onset is sudden and is revealed by pain and swelling. There is no local rise of temperature but discoloration of the skin is common. The blood may be rapidly or slowly absorbed. Recurrences are common. There may be any number of such hemorrhages or any one of them may be followed by destruction of the synovial membrane and bone with resulting ankylosis and deformity.

Other symptoms are those associated with the hemorrhage and depend on its location and severity. Even marked circulatory shock may occur in some instances. The spleen cannot be felt.

A characteristic history of similar symptoms in brothers, maternal male cousins, maternal granduncles, and so on, with sisters and maternal uncles exempt is usually obtained. A few instances of sporadic, nonhereditary hemophilia

have been described (Comby, Davidson and McQuarrie), but the evidence pointing to the spontaneous origin of hemophilia cannot be regarded as unequivocal.

BLOOD CHANGES.—The changes in the red cells and hemoglobin depend entirely on the duration and severity of blood loss and are similar to those described in the discussion of the posthemorrhagic anemias. At the time of hemorrhage there may be leukocytosis and the platelets are not infrequently increased. Blood platelets are never reduced in number. Bleeding time as carried out by Duke's method is usually normal, the thromboplastin of the tissue juice being sufficient to produce coagulation. During the bleeding phase of hemophilia, however, bleeding time may be prolonged. The clot retracts normally and the capillary resistance test is negative. Venipuncture, if skilfully executed, is without danger, the elasticity of the vessel wall being sufficient to close the wound.

The characteristic blood change in hemophilia is the prolongation of coagulation time and prothrombin time which may be as long as several hours. For the performance of these tests the methods of Howell, already described (Chapter II, this section) should be followed. It is very important that the drawn blood be not mixed with tissue juice since this will vitiate the result. It is a peculiar characteristic of hemophilic blood that coagulation time may vary considerably and at times may be nearly normal.

Diagnosis.—The diagnosis of hemophilia is in most instances rendered easy by the discovery of such characteristic features as a history of hereditary and familial occurrence, direct female transmission and male manifestation from the time of childhood, prolonged coagulation and prothrombin times and normal platelet count, bleeding time and clot retraction. Where such information is not obtainable or has not been elicited, confusion with several important conditions may arise.

Before the blood has been examined, a deep hematoma may be mistaken for a suppurative condition and surgical drainage may be attempted only to be followed by unexpected and often serious results. The joint manifestations of hemophilia may suggest a number of conditions, notably joint tuberculosis. In the latter instance, however, onset is slow, only one joint is usually affected, there is usually atrophy of the muscles above and below the joint, local rise of temperature is present and subcutaneous discoloration is absent. Bleeding elsewhere will suggest local causes such as kidney tumor, pulmonary disease and so on. In the case of prolonged epistaxis local causes may be sought. It should be borne in mind that hereditary multiple angiectases (familial epistaxis, Christian) may cause severe, prolonged blood loss.

Of the hemorrhagic diseases which may be confused with hemophilia, essential thrombocytopenic purpura is most noteworthy. Hereditary manifestations are very unusually encountered in this disease, both males and females may be affected, blood platelets are markedly reduced in number, bleeding time is prolonged, clot retraction is imperfect and both coagulation time and prothrombin time are normal. With careful physical and blood examination other forms of purpura such as that associated with aplastic anemia, acute leukemia, infections, intoxications, radiation, avitaminosis and the anaphylactoid purpuras should be readily ruled out. In melena neonatorum, although coagulation time is delayed, the very early occurrence of the disease, the lack of any evidence of heredity and the rapid and permanent recovery on appropriate treatment are important distinguishing features.

Several atypical and very rare forms of "hemorrhagic diathesis" which may be grouped under the heading *pseudohemophilia* have been described and in such cases exhaustive studies may be needed to reach a correct diagnosis. Rabe and Salomon, and Opitz and Frei described patients who bleed profusely from cuts and after slight trauma, apparently as the result of an absence of fibrinogen (*fibrinopenia*). Blood fibrinogen may be reduced as the result of damage to the liver, as occurs in atrophic cirrhosis, or in phosphorus or chloroform poisoning. Bernuth has described a condition in which there is failure of the capillaries to close. Blood findings in these cases may be the same as in true hemo-

philia. Glanzmann has described an hereditary pseudohemophilia in which the platelets are abnormal (*thrombasthenia*). Minot described a chronic familial hemorrhagic condition which, unlike true hemophilia, may occur in father and son and which is associated with prolonged bleeding time. Hess reported a patient who presented all the symptoms of hemophilia but in whom calcium deficiency appeared to be the cause of bleeding (*hemophilia calcipriva*).

Treatment.—There is no cure for hemophilia. It would be possible to eliminate this constitutional anomaly by proper restriction of marriage, or at least of propagation. Such measures cannot at present be carried out by law but at least patients and their families should be properly advised. Only unaffected males can marry with any assurance that the hemorrhagic tendency will not be transmitted. Although it is true that only one-half of the daughters of a female carrier inherit the trait and are able to transmit it, there is no way of distinguishing the normal daughters from the bearers of this hereditary anomaly.

Prevention of hemorrhage occupies first place in the treatment of this disease, which, of course, means that all male children of tainted stock must be protected most carefully from wounds and abrasions alike. As the child grows older he **should be informed of his inherited tendency and be taught to protect himself** in every way possible. In this way only a limited amount of security can be obtained as obviously in childhood and maturity alike open wounds, abrasions and bruises cannot be escaped. It is hardly necessary to state that in hemophilic children or children that are believed to be tainted, even the most trivial operations **should be avoided** so far as is humanly possible. This fact was recognized by the ancient Jews in relation to the rite of circumcision and even at that time there were rules laid down evidently intended to protect individuals of this class.

Immediately before operations of any sort **blood transfusion should be performed** with the view to protecting the patient by supplying normal platelets. This measure is followed by a decrease in the coagulation time, an effect which begins to disappear, however, in three days, the probable length of life of blood platelets (Minot and Lee). **Whole blood transfusions** are to be preferred.

In an actual attack the patient should be kept as **quiet** as possible and relieved, as far as may be, of fear and nervous disturbances. In many instances it is wise to give small doses of an **opiate** in order to do away with the dread of impending death which so many of these patients very naturally experience. Practically all of the surgical means usually employed to control hemorrhage, such as ligation of vessels, cauterization, application of pressure and the like, prove wholly futile. Styptics have been used as well as strong solutions of cocaine and adrenaline hydrochloride with variable effect. The objection to this last procedure is obvious in that if the hemorrhage is not wholly controlled within a short time the after-effect of the drug will be such as to promote relaxation of the vessels and an aggravation of the original hemorrhage.

Jay McLean and others have strongly recommended the use of **cephalin**, a substance obtained from the tissue juices, which is probably responsible for the prompt clotting of hemophilic blood when mixed with such juices. McLean emphasizes the fact that cephalin loses its thromboplastic power if exposed to the air and states that after an interval of two or three months it becomes wholly worthless. Obviously, therefore, a fresh specimen should be prepared whenever possible and kept *in vacuo*. A number of preparations of **thromboplastic substance** which fulfill these requirements have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association (New and Non-official Remedies, 1929). If these preparations are not available, **cotton-wool soaked in fresh normal blood or blood serum** should be applied to the wound. Before any preparation is applied **all blood clots** should be carefully **removed**, thus permitting the thromboplastic substance to be placed directly upon the oozing surfaces.

As general measures various forms of serum injections have been used with some degree of success, but whenever possible whole blood transfusions should be

given. If the local measures described are insufficient, the latter, frequently repeated, will be found to give the most prompt and constant results. The gelatin treatment of Sahli, which enjoyed quite a vogue for several years, seems to have been wholly abandoned and at the present time is not accredited with any decided beneficial results. The internal administration of cephalin has been attempted, apparently without convincing results, although slight decrease in the coagulation time has evidently occurred in certain instances.

Prognosis.—The mortality in this disease is extremely heavy and the majority of the affected male children of hemophilic families die before they reach ten years of age. As has been stated previously, certain children of tainted stock escape wholly and in the case of other individuals the disease appears only in a mild form. The tendency to bleed distinctly diminishes as the hemophilia grows older. Between attacks of hemorrhage the patient may be perfectly well or may be handicapped by deformities resulting from joint ankylosis. The immediate prognosis in a case of severe hemorrhage is always grave.

Pathology.—There are no characteristic findings except for the pathologic changes caused by the hemorrhages.

HEMORRHAGIC DISEASE OF THE NEWLY-BORN

Synonyms.—*Melena neonatorum*, hemorrhagic diathesis of the newly-born, hemophilia neonatorum, morbus hemorrhagica neonatorum.

Definition.—This is a condition which occurs only in infants in the first few days of life and is characterized by spontaneous hemorrhages and either a fatal termination or permanent recovery.

Etiology.—The hemorrhagic disease of the newly-born is said to occur in about 1 per cent of all newly-born infants (Rodda, McCollum) of both sexes. There is no hereditary or familial factor. There is no evidence that injury, infection or disease bear any etiologic relationship. The bleeding may commence at any time during the first week or two of life, usually about the fourth day and scarcely ever later than the twelfth day. The remarkable influence of blood transfusions on the course of the disease suggests some temporary defect of the infant's blood. Largely because of the rapid onset of the hemorrhages and their early termination in death or rapid response to treatment, blood studies have been conflicting and inadequate. Whipple and later Gelston found a deficiency of prothrombin in the blood. The studies of Kugelmass and his associates, of Moore and Brodie, and of Brown and Tisdall suggest that the partaking of a defective diet by the mother may be etiologically related to this tendency to bleed.

Symptomatology.—Bleeding is spontaneous and may be in the skin or subcutaneous tissues, from the intestines or the umbilical cord, in the brain or meninges, or from mucous and serous surfaces, lungs, kidneys or retina. Hemorrhages are usually multiple. Symptoms depend on the location and severity of the bleeding and may be so slight as to attract no attention or be so severe as to cause sudden death. There may be simple loss of appetite, listlessness or failure to gain weight. Pallor, collapse and coldness of the extremities may be the only evidence of serious internal hemorrhage. Drowsiness, vomiting, frequent convulsive seizures and marked respiratory embarrassment may supervene and indicate cerebral or meningeal hemorrhage.

Physical findings are similarly variable. Petechiae or large ecchymoses may be found in the skin or subcutaneous tissues. There may be free bleeding or simply oozing from the umbilical cord. Large hematmata may appear on the head. Pallor, restlessness, dyspnea and cold extremities may be absent or marked. Local or generalized rigidity or paralysis or convulsions may appear.

LABORATORY FINDINGS.—*Blood.*—Changes in the red cells or hemoglobin are only those produced by the blood loss. Blood platelets are about normal in number according to the meager reports available. The coagulation time as well as the bleeding time was found prolonged by Rodda and by Lucas and his associates. These findings, however, were not confirmed by Beveridge.

Blood is frequently found in the stools and should be distinguished from meconium. The *urine, vomitus or cerebrospinal fluid* may reveal the presence of blood.

Diagnosis.—Blood may be swallowed from the fissured nipple of the mother and be subsequently vomited or appear in the stool. Hemophilia and essential thrombocytopenic purpura rarely make their appearance in the first few days of life. The marked reduction in the number of blood platelets in the latter disease and the hereditary feature of the former condition usually readily serve to differentiate them. Furthermore, both bleeding from the umbilical cord and melenas are unusual in hemophilia. Where hemorrhage is entirely internal, diagnosis may be more difficult and the acumen of the physician may be greatly taxed.

Treatment.—Royster suggests that as a mode of prevention the coagulation time of all newly-born infants be taken, and if this is longer than 10 minutes he advises the injection of blood. For the actual bleeding, **subcutaneous injections of whole human blood**, 20 to 30 c.c. every 3 to 6 hours, have been employed, but **blood transfusions** are far more satisfactory in their results. Rarely more than one transfusion is necessary. If the condition is urgent, blood from one of the parents may be given without matching since agglutinins as a rule are not developed in young infants. About 15 c.c. of blood per pound of body weight may be given into the superior longitudinal sinus, external jugular vein or the internal saphenous vein over the internal malleolus. The injection should be slowly made.

Prognosis.—The course of the illness is rapid. Death occurs in three days or less or spontaneous recovery may take place. The use of blood transfusions has reduced the mortality from 70 to 80 per cent to 10 per cent or less.

Pathology.—Autopsy findings are those due to hemorrhage. Rarely ulceration has been found in the alimentary tract, but usually only hyperemia, congestion and punctiform hemorrhages are noted.

BIBLIOGRAPHY

Purpura

- ALEXANDER, H. L. AND ETERMANN, C. H.: Allergic purpura, *J. Am. M. Ass.*, 92: 2092-2094, 1929.
- ASCHOFF, L.: Lectures on Pathology, New York, Paul B. Hoeber, Inc., 1924.
- BEDSON, S. P.: Role of reticulo-endothelial system in regulation of number of platelets in circulation, *Brit. J. Exper. Path.*, 7: 317-324, 1926.
- CHRISTIAN, H. A.: Visceral disturbances in patients with cutaneous lesions of the erythema group, *J. Am. M. Ass.*, 69: 325-329, 1917.
- : *Purpura*, Oxford Medicine, New York, Oxford University Press, 2: 779-797, 1920.
- EMILE-WEIL, P. AND ISCH-WALL, P.: Pathogénie de l'hémogénie, *Presse méd.*, 31: 243-245, 1923.
- FRANK, E.: Die essentielle Thrombopenie, *Berl. klin. Wchnschr.*, 52: 454; 490, 1915.
- GLANZMANN, E.: Hereditäre hämorrhagische Thrombasthenie, *Jahrb. f. Kinderh.*, 88: 113-141, 1918.
- VAN GOIDSENHOVEN, F.: Le traitement de la thrombopénie essentielle par la ligature de l'artère splénique, *Revue belge des Sciences Médicales*, 1: 97-143, 1929.
- GRAM, H. C.: Purpura cured by shock treatment, *Ztschr. f. klin. Med.*, 95: 51-65, 1922.
- HENOCHE, E.: Ueber eine eigenthümliche Form von Purpura, *Berl. klin. Wchnschr.*, 11: 641-643, 1874.
- HESS, A. F.: The blood and blood vessels in hemophilia and other hemorrhagic diseases, *Arch. Int. Med.*, 18: 203-220, 1916.
- : A consideration of the reduction of the blood platelets in purpura, *Proc. Soc. Exper. Biol. & Med.*, 14: 96, 1916-1917.
- KAHN, I. S.: Henoch's purpura due to food allergy, *J. Lab. & Clin. Med.*, 14: 835, 1929.
- KAZNELSON, P.: Verschwinden der hämorrhagischen Diathese bei einem Fälle von essentielle Thrombopenie (Frank) nach Milzexstirpation, *Wien. klin. Wchnschr.*, 29: 1451-1454, 1916.
- : Thrombolytische Purpura, *Ztschr. f. klin. Med.*, 87: 133-164, 1919.
- KILLINS, W. A.: Acute thrombocytopenic purpura cured by splenectomy, *J. Am. M. Ass.*, 92: 1832, 1929.
- KROGH, A.: *The Anatomy and Physiology of the Capillaries*, New Haven, Yale University Press, 1922.
- LEEDS, C.: Hautblutungen durch Stauung, hervorgerufen als diagnostisches Hilfsmittel beim Scharlach, *München. med. Wchnschr.*, 58: 293-295, 1911.
- LESCHKE, E.: Klinik und Pathogenese der thrombopenischen Purpura (Werhofsche Krankheit), *Deutsche med. Wchnschr.*, 51: 1352-1355, 1925.
- AND WITTKOWER, E.: Die Werhofsche Blutflecken-Krankheit, *Ztschr. f. klin. Med.*, 102: 6-744, 1926.
- LIEBLING, P.: Purpura hemorrhagica complicating pregnancy; both mother and child were affected and recovered, *Am. J. Obst. & Gynec.*, 11: 847-850, 1926.
- MORRISON, M., LEDERER, M. AND FRADKIN, W. Z.: Accessory spleens: their significance in essential thrombocytopenic purpura hemorrhagica, *Am. J. M. Sc.*, 176: 672-681, 1928.

- OSLER, W.: The visceral lesions of purpura and allied conditions, *Brit. M. J.*, 1: 517-525, 1914.
- PEPPER, O. H. P.: Hematology of subacute streptococcus viridans endocarditis, *J. Am. M. Ass.*, 89: 1377-1380, 1927.
- PRATT, J. H.: Purpura and Hemophilia, Osler and McCrae, *Modern Medicine*, Chap. 3, Philadelphia, Lea & Febiger, 5: 1927.
- REUBEN, M. S. AND CLAMAN, L.: Splenectomy in acute thrombocytopenic purpura hemorrhagica, *Arch. Pediat.*, 45: 84-97, 1928.
- ROSENTHAL, N.: The blood picture in purpura, *J. Lab. & Clin. Med.*, 18: 303-322, 1928.
- ROSKAM, J.: Pathogénie de la prolongation des hémorragies dans les syndromes hémogéniques et dans l'hémophilie vraie, *Presse méd.*, 31: 972-976, 1923.
- SCHOENLEIN, J. L.: Allgemeine und spezielle Pathologie und Therapie, 2: 45, 1837.
- SCHULTZ, W.: Die Purpuraerkrankungen, *Ergebn. d. inn. Med. u. Kinderh.*, 16: 32-106, 1919.
- SEELIGER, S.: Thrombopenia and aleukia, *Klin. Wchnschr.*, 3: 731-735, 1924.
- SOOY, J. W. AND MOISE, T. S.: Treatment of idiopathic purpura hemorrhagica by exposure to mercury vapor quartz lamp, *J. Am. M. Ass.*, 87: 94, 1926.
- SPENCE, A. W.: The results of splenectomy for purpura haemorrhagica, *Brit. J. Surg.*, 15: 466-499, 1928.
- WERLHOFF, P. G.: Opera medica, Hannoverae, imp. fratrum Helwinglorum, 2: 615, 1775-1776.
- WHIPPLE, A. O.: Splenectomy as a therapeutic measure in thrombocytopenic purpura haemorrhagica, *Surg. Gynec. & Obst.*, 42: 329-341, 1926.

Hemophilia

- ADDIS, T.: The pathogenesis of hereditary haemophilia, *J. Path. & Bact.*, 15: 427-452, 1910-1911.
- VON BERNUTH, F.: Ueber das Verhalten von Kapillaren bei Blutungsübeln insbesondere bei der Hämophilie, *Arch. f. Kinderh.*, 76: 54-63, 1925.
- BULLOCH, W. AND FILDES, P.: Hemophilia, London University, Francis Galton Laboratory for National Eugenics, Treasury of Human Inheritance, 1: 169, 1912.
- CHRISTIAN, H. A.: Purpura, Oxford Medicine, New York, Oxford University Press, p. 779, 1920.
- COMBY, J.: La question de l'hémophilie, *Arch. de med. d. enf.*, 29: 413-416, 1926.
- DAVIDSON, E. C. AND McQUARRIE, I.: Hemophilia, a study of the blood, the clinical course and the heredity in three cases, *Bull. Johns Hopkins Hosp.*, 36: 343-356, 1925.
- GLANZMANN, E.: Hereditäre hämorrhagische Thrombopathie, ein Beitrag zur Pathologie der Blutplättchen, *Jahrb. f. Kinderh.*, 88: 113-141, 1918.
- GROSSOT, E.: Zur lehre von der Hämophilie, *Ztschr. f. klin. Med.*, 76: 194-218, 1912.
- HESS, A. F.: The calcium factor in hemophilia, a case with calcium deficiency (calciopriva), *Bull. Johns Hopkins Hosp.*, 26: 872-876, 1915.
- HOWELL, W. H.: Condition of the blood in hemophilia, thrombosis and purpura, *Arch. Int. Med.*, 13: 76-95, 1914.
- AND CEKADA, E. B.: The cause of the delayed clotting of hemophilic blood, *Am. J. Physiol.*, 78: 500-511, 1926.
- LEGG, J. W.: A Treatise on Haemophilia, London, H. K. Lewis, 1872.
- LOYD, B. L.: Actual pedigree of hemophilia, *Eugenical News*, 11: 179, 1926.
- MACKLIN, M. T.: Heredity in hemophilia, *Am. J. M. Sc.*, 175: 218-224, 1928.
- MCLEAN, JAY: Hemophilia, Oxford Medicine, Oxford University Press, 2: 799-817, 1920.
- MINOT, G. R.: A familial haemorrhagic condition associated with prolongation of the bleeding time, *Med. Press*, 126: 56-59, 1928.
- AND LEE, R. I.: The blood platelets in hemophilia, *Arch. Int. Med.*, 17: 474-495, 1916.
- NASSE, C. F.: Von einer erblichen Neigung zu tödlichen Blutungen, *Arch. f. med. Erfahr.*, 1: 385-434, 1820.
- OPITZ, H. AND FREI, M.: Ueber eine neue Form der Pseudohämophilie, *Jahrb. f. Kinderh.*, 44: 374-389, 1921.
- PRATT, J. H.: Haemophilia, *Modern Medicine*, Osler and McCrae, Philadelphia, Lea & Febiger, 5: 127, 1927.
- RABE, F. AND SALOMON, E.: Ueber Faserstoffmangel im Blute bei einem Falle von Hämophilie, *Deutsches Arch. f. klin. Med.*, 132: 240-244, 1920.
- WRIGHT, A. E.: On a method of determining the condition of blood coagulability for clinical and experimental purposes, and on the effect of the administration of calcium salts in haemophilia and actual or threatened haemorrhage, *Brit. M. J.*, 2: 223-225, 1898.

Hemorrhagic Disease of the Newly-born

- BEVERIDGE, R. S.: Haemorrhagic diseases of the newborn, *Arch. Dis. Child.*, 3: 39-48, 1928.
- BROWN, A. AND TISDALL, F. F.: Antirachitic effect of December sunlight; seasonal variation, *Proc. Soc. Exper. Biol. & Med.*, 24: 446-449, 1927.
- GELSTON, C. F.: On the etiology of hemorrhagic disease of the new-born, *Am. J. Dis. Child.*, 22: 351-357, 1921.
- KUGELMASS, I. N. AND TRITSCH, J. E.: Prenatal prevention of potential hemorrhagic disease of the new-born, *J. Am. M. Ass.*, 92: 531, 1929.
- , BANCROFT, F. W. AND STANLEY-BROWN, M.: Determination and regulation of blood clotting function in childhood, *Am. J. Dis. Child.*, 39: 471-486, 1930.
- LUCAS, W. P., DEARING, B. F., HOOBLE, H., COX, A., JONES, M. AND SMYTH, F. S.: Blood studies in the new-born, *Am. J. Dis. Child.*, 22: 525-529, 1921.
- MCCOLLUM, J. L.: Idiopathic haemorrhage of the new-born, *Canad. M. A. J.*, 18: 550-554, 1928.
- MOORE, C. U. AND BRODIE, J. L.: The relation of maternal diet to hemorrhage in the new-born, *Am. J. Dis. Child.*, 34: 53-60, 1927.
- RODDA, F. C.: Studies with a new method for determining the coagulation time of the blood in the new-born, *Am. J. Dis. Child.*, 19: 269-276, 1920.
- : The coagulation time of blood in the new-born; with especial reference to cerebral hemorrhage, *J. Am. M. Ass.*, 75: 452-457, 1920.
- ROYSTER, L. T.: Hemorrhagic disease of the new-born, *Virginia M. Monthly*, 51: 693-697, 1924-1925.

THIS BOOK IS DUE ON THE LAST DATE
STAMPED BELOW

BOOKS REQUESTED BY ANOTHER BORROWER
ARE SUBJECT TO IMMEDIATE RECALL

HEALTH SCIENCES LIBRARY
UNIVERSITY OF CALIFORNIA, DAVIS

Book Slip-Series 1667